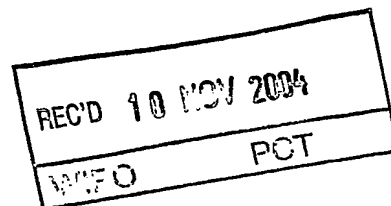


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CHEMICAL COMPOUNDS

The present invention relates to novel compounds, and pharmaceutically acceptable salts thereof, which inhibit basic carboxypeptidases, more specifically carboxypeptidase U, and thus can be used in the prevention and treatment of diseases wherein inhibition of carboxypeptidase U is beneficial, such as thrombosis and hypercoagulability in blood and tissue, atherosclerosis, adhesions, dermal scarring, cancer, fibrotic conditions, inflammatory diseases and those conditions which benefit from maintaining or enhancing bradykinin levels in the body. In further aspects, the invention relates to compounds of the invention for use in therapy; to processes for preparation of such new compounds; to pharmaceutical compositions containing at least one compound of the invention, or a pharmaceutically acceptable salt thereof, as active ingredient; and to the use of the active compounds in the manufacture of medicaments for the medical use indicated above.

Fibrinolysis is the result of a series of enzymatic reactions resulting in the degradation of fibrin by plasmin. The activation of plasminogen is the central process in fibrinolysis. The cleavage of plasminogen to produce plasmin is accomplished by the plasminogen activators, tissue-type plasminogen activator (t-PA) or urokinase-type plasminogen activator (u-PA). Initial plasmin degradation of fibrin generates carboxy-terminal lysine residues that serve as high affinity binding sites for plasminogen. Since plasminogen bound to fibrin is much more readily activated to plasmin than free plasminogen this mechanism provides a positive feedback regulation of fibrinolysis.

One of the endogenous inhibitors to fibrinolysis is carboxypeptidase U (CPU). CPU is also known as plasma carboxypeptidase B, active thrombin activatable fibrinolysis inhibitor (TAFIa), carboxypeptidase R and inducible carboxypeptidase activity. CPU is formed during coagulation and fibrinolysis from its precursor proCPU by the action of proteolytic enzymes, such as thrombin, thrombin-thrombomodulin complex or plasmin. CPU cleaves basic amino acids at the carboxy-terminal of fibrin fragments. The loss of carboxy-terminal lysines and thereby of lysine binding sites for plasminogen then serves to inhibit fibrinolysis. By inhibiting the loss of lysine binding sites for plasminogen and thus increase the rate of plasmin formation, effective inhibitors of carboxypeptidase U are expected to facilitate fibrinolysis.

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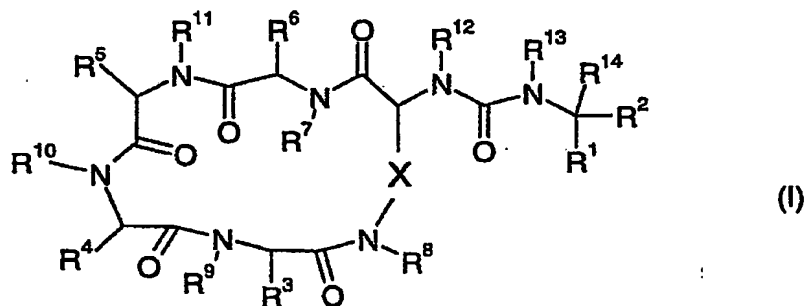
2-Mercaptomethyl-3-guanidinoethylthiopropionic acid is reported as a carboxypeptidase N inhibitor. More recently, this compound has been shown to inhibit CPU, Hendriks, D. *et al.*, Biochimica et Biophysica Acta, 1034 (1990) 86-92.

Guanidinoethylmercaptosuccinic acid is reported as a carboxypeptidase N inhibitor. More recently, this compound has been shown to inhibit CPU, Eaton, D. L., *et al.*, The Journal of Biological Chemistry, 266 (1991) 21833-21838.

CPU inhibitors are disclosed in WO 00/66550, WO 00/66557, WO 03/013526 and WO 03/027128 and a pharmaceutical formulation containing a CPU inhibitor and a thrombin inhibitor is disclosed in WO 00/66152. Inhibitors of plasma carboxypeptidase B are disclosed in WO 01/19836. Inhibitors of TAFIa are disclosed in WO 02/14285, WO 03/061652 and WO 03/061653.

Cyclic Anabaenopeptin-type peptides are disclosed in: Tetrahedron Letters, Vol. 36, No. 9, pp. 1511-1514 (1995); J. Org. Chem. (1997) 62 6199-6203; Tetrahedron Letters, Vol. 36, No. 33, pp. 5933-5936, (1995); J. Nat. Prod. (1996) 59 570-575; Tetrahedron Letters, Vol. 38, No. 31, pp. 5525-5528, (1997); J. Nat. Prod. (1997) 60 139-141; Tetrahedron 54 (1998) 6719-6724; Bioorganic & Medicinal Chemistry Letters 9 (1999) 1243-1246; Tetrahedron 56 (2000) 725-733; J. Nat. Prod. (2000) 63 1280-1282; J. Nat. Prod. (2001) 64 No. 8 1053; Tetrahedron 58 (2002) 6863-6871; and, J. Nat. Prod. (2002) 65 1187-1189.

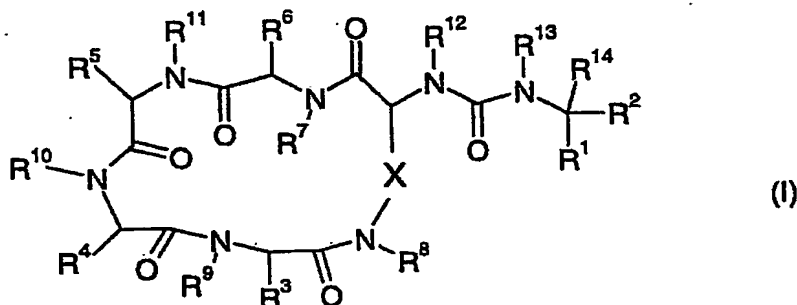
It has now been found that compounds of formula (I):



or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, are particularly effective as inhibitors of carboxypeptidase U and are therefore useful as medicaments for the treatment or prophylaxis of conditions wherein inhibition of carboxypeptidase U is beneficial, for example in the treatment or prophylaxis of: thrombosis and/or hypercoagulability in blood and/or tissues; atherosclerosis; adhesions;

dermal scarring; cancer; fibrotic conditions; inflammatory diseases; conditions which benefit from maintaining or enhancing bradykinin levels in the body of a mammal (such as man); protein C resistance; inherited or acquired deficiencies in antithrombin III, protein C, protein S or heparin cofactor II; circulatory or septic shock; circulating antiphospholipid antibodies; hyperhomocysteinemia; heparin induced thrombocytopenia; defects in fibrinolysis; venous thrombosis; pulmonary embolism; arterial thrombosis (for example in myocardial infarction, unstable angina, thrombosis-based stroke or peripheral arterial thrombosis); systemic embolism usually from the atrium during atrial fibrillation or from the left ventricle after transmural myocardial infarction; the prophylaxis of re-occlusion and restenosis (that is, thrombosis) after thrombolysis; percutaneous trans-luminal intervention (PTI) and coronary bypass operations; the prevention of re-thrombosis after microsurgery and vascular surgery in general; disseminated intravascular coagulation caused by bacteria, multiple trauma, intoxication or any other mechanism; fibrinolytic treatment when blood is in contact with foreign surfaces in the body, such as vascular grafts, vascular stents, vascular catheters, mechanical and biological prosthetic valves or any other medical device; fibrinolytic treatment when blood is in contact with medical devices outside the body, such as during cardiovascular surgery using a heart-lung machine or in haemodialysis; prophylaxis of atherosclerotic progression and/or transplant rejection in patients subject to organ transplantation, for example renal transplantation; inhibiting tumor maturation and progression; any condition in which fibrosis is a contributing factor (for example cystic fibrosis, pulmonary fibrotic disease eg chronic obstructive pulmonary disease (COPD), adult respiratory distress syndrome (ARDS), fibromuscular dysplasia, fibrotic lung disease or fibrin deposits in the eye during ophthalmic surgery); inflammation (such as asthma, arthritis, endometriosis, inflammatory bowel diseases, psoriasis or atopic dermatitis); neurodegenerative diseases such as Alzheimers and Parkinsons; or conditions known to benefit from maintaining or enhancing bradykinin levels (such as hypertension, angina, heart failure, pulmonary hypertension, renal failure or organ failure).

Thus, the present invention provides the use of a compound of formula (I):



wherein:

X is $(CH_2)_m Y (CH_2)_n$;

m and n are, independently, 1, 2, 3, 4, 5 or 6; provided that m + n is not more than 6;

5 Y is a bond, O, S(O)_p, or S-S;

R¹ is CO₂R¹⁵ or a carboxylic acid isostere such as S(O)₂OH, S(O)₂NHR¹⁵, PO(OR¹⁵)OH, PO(OR¹⁵)NH₂, B(OR¹⁵)₂, PO(R¹⁵)OH, PO(R¹⁵)NH₂ or tetrazole;

10 R², R³, R⁴, R⁵ and R⁶ are, independently, hydrogen, C₁₋₆ alkyl (optionally substituted by halogen, hydroxy, cyano, SH, S(O)₃H, S(O)₄(C₁₋₆ alkyl), OC(O)(C₁₋₄ alkyl), CF₃, C₁₋₄ alkoxy, OCF₃, COOH, CONH₂, CONH(C₁₋₆ alkyl), NH₂, CNH(NH₂), or NHCNH(NH₂)), C₃₋₆ cycloalkyl(C₁₋₄)alkyl (wherein the cycloalkyl ring is optionally substituted by halogen, hydroxy, cyano, C₁₋₄ alkyl, CF₃, C₁₋₄ alkoxy, OCF₃, NH₂, CNH(NH₂) or NHCNH(NH₂)), heterocyclyl(C₁₋₄)alkyl (wherein the heterocyclyl ring is optionally substituted by halogen, hydroxy, cyano, C₁₋₄ alkyl, CF₃, C₁₋₄ alkoxy, OCF₃, NH₂, CNH(NH₂) or NHCNH(NH₂)),

15 phenyl(C₁₋₄)alkyl (wherein the phenyl ring is optionally substituted by halogen, hydroxy, cyano, C₁₋₄ alkyl, CF₃, C₁₋₄ alkoxy, OCF₃, NH₂, CNH(NH₂) or NHCNH(NH₂)) or heteroaryl(C₁₋₄)alkyl (wherein the heteroaryl ring is optionally substituted by halogen, hydroxy, cyano, C₁₋₄ alkyl, CF₃, C₁₋₄ alkoxy, OCF₃, NH₂, CNH(NH₂) or NHCNH(NH₂));

p and q are, independently, 0, 1 or 2;

20 R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹² and R¹³ are, independently, H or C₁₋₄ alkyl;

R¹⁴ is H or C₁₋₄ alkyl; and,

R¹⁵ is H or C₁₋₄ alkyl;

or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt; in a method of manufacturing a medicament for the treatment or prophylaxis of a condition wherein inhibition of carboxypeptidase U is beneficial, for example in the treatment or prophylaxis of: thrombosis and/or hypercoagulability in blood and/or tissues;

atherosclerosis; adhesions; dermal scarring; cancer; fibrotic conditions; inflammatory diseases; conditions which benefit from maintaining or enhancing bradykinin levels in the body of a mammal (such as man); protein C resistance; inherited or acquired deficiencies in antithrombin III, protein C, protein S or heparin cofactor II; circulatory or septic shock; circulating antiphospholipid antibodies; hyperhomocysteinemia; heparin induced thrombocytopenia; defects in fibrinolysis; venous thrombosis; pulmonary embolism; arterial thrombosis (for example in myocardial infarction, unstable angina, thrombosis-based stroke or peripheral arterial thrombosis); systemic embolism usually from the atrium during atrial fibrillation or from the left ventricle after transmural myocardial infarction; the prophylaxis of re-occlusion and restenosis (that is, thrombosis) after thrombolysis; percutaneous trans-luminal intervention (PTI) and coronary bypass operations; the prevention of re-thrombosis after microsurgery and vascular surgery in general; disseminated intravascular coagulation caused by bacteria, multiple trauma, intoxication or any other mechanism; fibrinolytic treatment when blood is in contact with foreign surfaces in the body, such as vascular grafts, vascular stents, vascular catheters, mechanical and biological prosthetic valves or any other medical device; fibrinolytic treatment when blood is in contact with medical devices outside the body, such as during cardiovascular surgery using a heart-lung machine or in haemodialysis; prophylaxis of atherosclerotic progression and/or transplant rejection in patients subject to organ transplantation, for example renal transplantation; inhibiting tumor maturation and progression; any condition in which fibrosis is a contributing factor (for example cystic fibrosis, pulmonary fibrotic disease eg chronic obstructive pulmonary disease (COPD), adult respiratory distress syndrome (ARDS), fibromuscular dysplasia, fibrotic lung disease or fibrin deposits in the eye during ophthalmic surgery); inflammation (such as asthma, arthritis, endometriosis, inflammatory bowel diseases, psoriasis or atopic dermatitis); neurodegenerative diseases such as Alzheimers and Parkinsons; or conditions known to benefit from maintaining or enhancing bradykinin levels (such as hypertension, angina, heart failure, pulmonary hypertension, renal failure or organ failure).

In the context of the present invention, the term "therapy" includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be understood accordingly.

In one particular aspect the present invention provides the use of a compound of formula (I), as herein described, in a method of manufacturing a medicament for the treatment or prophylaxis of thrombosis and/or hypercoagulability in blood and/or tissues; atherosclerosis; fibrotic conditions; inflammatory diseases; or a condition which benefits from maintaining or enhancing bradykinin levels in the body of a mammal (such as man).

In another aspect the present invention provides the use of a compound of formula (I), as herein described, in a method of manufacturing a medicament for the treatment or prophylaxis of thrombosis and/or hypercoagulability in blood and/or tissues; atherosclerosis; fibrotic conditions; or a condition which benefits from maintaining or enhancing bradykinin levels in the body of a mammal (such as man); for example a medicament for the treatment or prophylaxis of thrombosis and/or hypercoagulability in blood and/or tissues.

The compounds of formula (I) exist in isomeric forms and the present invention covers all such forms and mixtures thereof in all proportions. Both pure enantiomers, racemic mixtures and equal and unequal mixtures of two enantiomers are within the scope of the present invention. It should also be understood that all possible diastereomeric forms possible are within the scope of the invention.

Compounds of formula (I) can be in the form of a salt. Suitable salts include acid addition salts such as a hydrochloride, dihydrochloride, hydrobromide, phosphate, sulfate, acetate, diacetate, fumarate, maleate, tartrate, citrate, oxalate, methanesulfonate or *p*-toluenesulfonate. Salts also include metal salts, such as an alkali metal salt (for example a sodium or potassium salt) or an alkaline earth metal salt (for example magnesium or calcium).

The term C₁₋₄ alkyl denotes a straight or branched alkyl group having 1 to 4 carbon atoms in the chain. Examples of alkyl include methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl and *tert*-butyl.

The term C₁₋₄ alkoxy denotes an alkyl-O group, where alkyl is straight or branched chain and examples include methoxy and ethoxy.

Halogen includes fluoro, chloro, bromo and iodo (but is, for example, fluoro, chloro or bromo).

Cycloalkyl is, for example, cyclopropyl, cyclopentyl or cyclohexyl.

The term heterocyclyl denotes a non-aromatic ring containing carbon and at least one (such as one or two) atoms selected from nitrogen, oxygen or sulphur. Heterocyclyl is, for example, pyrrolidinyl, piperidinyl, piperazinyl or morpholinyl.

The term heteroaryl denotes an aromatic ring system (for example a mono-cycle or a bicycle) containing carbon and at least one (such as one or two) atoms selected from nitrogen, oxygen or sulphur. Heteroaryl, is for example, furan, thiophene, pyrrole, oxazole, isoxazole, thiazole, imidazole, pyrazole, isothiazole, oxadiazole, furazan, [1,2,3]-triazole, [1,2,4]-triazole, thiadiazole, pyridine, pyridazine, pyrimidine, pyrazine, indole or naphthyridine.

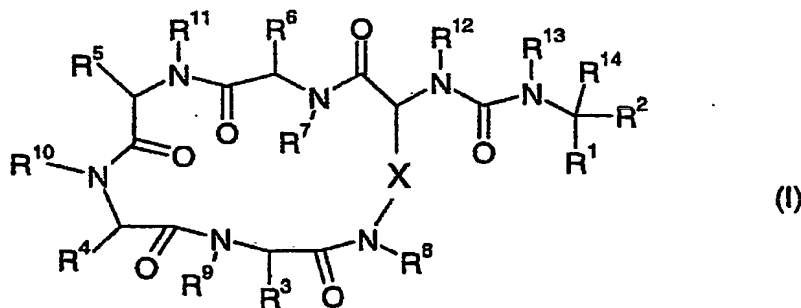
Phenylalkyl is for example benzyl or 1-phenyleth-2-yl.

Cycloalkylalkyl is, for example, cyclohexylmethyl.

Heteroalkylalkyl is, for example, indol-3-ylmethyl.

Heterocyclylalkyl is, for example, piperidin-1-ylmethyl.

In another aspect the present invention provides a compound of formula (I):



wherein:

X is (CH₂)₄;

R¹ is CO₂R¹⁵;

R² is straight-chain C₁₋₆ alkyl substituted at its terminus by NH₂, CNH(NH₂) or

NHCNH(NH₂); C₃₋₆ cycloalkyl substituted by NH₂, CNH(NH₂) or NHCNH(NH₂);

heterocyclyl containing at least one nitrogen atom; non-nitrogen containing heterocyclyl

substituted with NH₂, CNH(NH₂) or NHCNH(NH₂); heteroaryl substituted with NH₂,

CNH(NH₂) or NHCNH(NH₂); phenyl substituted with NH₂, CNH(NH₂) or NHCNH(NH₂);

heteroaryl(C₁₋₄)alkyl substituted with NH₂, CNH(NH₂) or NHCNH(NH₂); phenyl(C₁₋

4)alkyl substituted with NH₂, CNH(NH₂) or NHCNH(NH₂); or C₃₋₆ cycloalkyl(C₁₋₄)alkyl

substituted with NH₂, CNH(NH₂) or NHCNH(NH₂); all of the above rings being optionally

further substituted by one or more of: halogen, hydroxy, cyano, C₁₋₄ alkyl, CF₃, C₁₋₄ alkoxy or OCF₃;

one of R³, R⁴, R⁵ and R⁶ is independently, heteroaryl(C₁₋₄)alkyl (wherein the heteroaryl ring is optionally substituted by halogen, hydroxy, cyano, C₁₋₄ alkyl, CF₃, C₁₋₄

- 5 alkoxy, OCF₃, NH₂, CNH(NH₂) or NHCNH(NH₂)); and the others are, independently, hydrogen, C₁₋₆ alkyl (optionally substituted by halogen, hydroxy, cyano, SH, S(O)₃H, S(O)_q(C₁₋₆ alkyl), OC(O)(C₁₋₄ alkyl), CF₃, C₁₋₄ alkoxy, OCF₃, COOH, CONH₂, CONH(C₁₋₆ alkyl), NH₂, CNH(NH₂), or NHCNH(NH₂)), C₃₋₆ cycloalkyl(C₁₋₄)alkyl (wherein the cycloalkyl ring is optionally substituted by halogen, hydroxy, cyano, C₁₋₄ alkyl, CF₃, C₁₋₄
- 10 alkoxy, OCF₃, NH₂, CNH(NH₂) or NHCNH(NH₂)), heterocycl(C₁₋₄)alkyl (wherein the heterocycl ring is optionally substituted by halogen, hydroxy, cyano, C₁₋₄ alkyl, CF₃, C₁₋₄ alkoxy, OCF₃, NH₂, CNH(NH₂) or NHCNH(NH₂)), phenyl(C₁₋₄)alkyl (wherein the phenyl ring is optionally substituted by halogen, hydroxy, cyano, C₁₋₄ alkyl, CF₃, C₁₋₄ alkoxy, OCF₃, NH₂, CNH(NH₂) or NHCNH(NH₂)) or heteroaryl(C₁₋₄)alkyl (wherein the heteroaryl
- 15 ring is optionally substituted by halogen, hydroxy, cyano, C₁₋₄ alkyl, CF₃, C₁₋₄ alkoxy, OCF₃, NH₂, CNH(NH₂) or NHCNH(NH₂));

p and q are, independently, 0, 1 or 2;

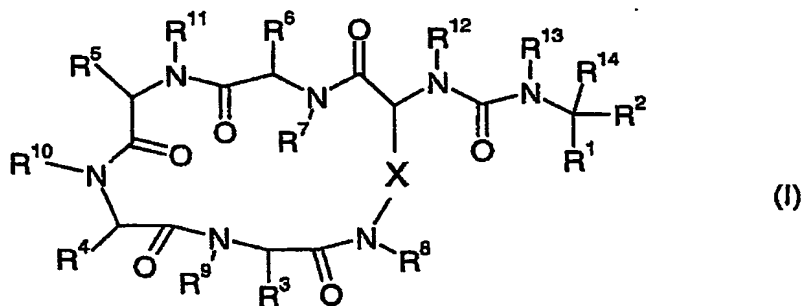
R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹² and R¹³ are, independently, H or C₁₋₄ alkyl;

R¹⁴ is H or C₁₋₄ alkyl; and,

- 20 R¹⁵ is H or C₁₋₄ alkyl;

or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt.

In a further aspect the present invention provides a compound of formula (I):

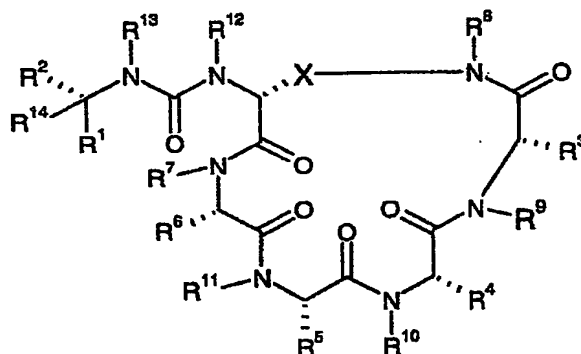


wherein:

- 25 R¹ is CO₂R¹⁵;

- R^2 is straight-chain C_{1-6} alkyl substituted at its terminus by NH_2 , $CNH(NH_2)$ or $NHCNH(NH_2)$; C_4 alkyl (such as $CH(CH_3)CH_2CH_3$ or $CH_2CH(CH_3)_2$); or (aminopyridinyl)methyl (for example (6-aminopyridin-3-yl)methyl); one of R^3 and R^4 is (indol-3-yl) CH_2 optionally substituted by halo or hydroxy; and the other is benzyl (optionally substituted by halo or hydroxy) or C_4 alkyl (such as $CH(CH_3)CH_2CH_3$ or $CH_2CH(CH_3)_2$); or R^3 and R^4 are both methyl;
- R^5 and R^6 are, independently, C_{1-6} alkyl (for example CH_3 , $CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$ or $CH_2CH(CH_3)_2$);
- R^7 , R^8 , R^9 , R^{11} , R^{12} , R^{13} and R^{14} are H;
- R^{10} is C_{1-4} alkyl; and,
- R^{15} is H or C_{1-4} alkyl.

In another aspect the present invention provides a compound of formula (I) having the chirality shown below:



In an aspect of the invention X is $(CH_2)_4$.

In a further aspect of the invention R^1 is CO_2R^{15} wherein R^{15} is H or C_{1-4} alkyl (for example methyl).

In another aspect R^2 is straight-chain C_{1-6} alkyl substituted at its terminus by NH_2 , $CNH(NH_2)$ or $NHCNH(NH_2)$; C_4 alkyl (such as $CH(CH_3)CH_2CH_3$ or $CH_2CH(CH_3)_2$); or (aminopyridinyl)methyl (for example (6-aminopyridin-3-yl)methyl).

In a still further aspect of the invention R^2 is C_{1-6} alkyl (such as iso-propyl, $CH(CH_3)CH_2CH_3$ or $CH_2CH(CH_3)_2$), benzyl, or straight-chain C_{1-6} alkyl substituted at its terminus by NH_2 , $CNH(NH_2)$, $NHCNH(NH_2)$ or (6-aminopyridin-3-yl)methyl. In another

aspect R^2 is straight-chain C_{1-6} alkyl substituted at its terminus by NH_2 , $CNH(NH_2)$, $NHCNH(NH_2)$ or (6-aminopyridin-3-yl)methyl.

In yet another aspect of the invention R^3 is CH_2 indolyl (wherein the indolyl is optionally substituted by one or more of: halogen (for example chloro or bromo) or hydroxy), C_{1-4} alkyl or benzyl (optionally substituted by halogen (for example bromo) or hydroxy).

In another aspect of the invention R^4 is CH_2 indolyl (wherein the indolyl is optionally substituted by one or more of: halogen (for example chloro or bromo) or hydroxy), C_{1-6} alkyl (such as methyl, iso-propyl, $CH(CH_3)CH_2CH_3$ or $CH_2CH(CH_3)_2$) or benzyl (optionally substituted by halogen (for example bromo) or hydroxy).

In a further aspect of the invention R^5 and R^6 are, independently, C_{1-6} alkyl (such as methyl, iso-propyl, $CH(CH_3)CH_2CH_3$ or $CH_2CH(CH_3)_2$).

In another aspect of the invention R^7 , R^8 , R^9 , R^{11} , R^{12} , R^{13} and R^{14} are all H.

In yet another aspect of the invention R^{10} is C_{1-4} alkyl (for example methyl).

In a still further aspect the invention provides a compound of formula (I) which is Compound 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or 16, of a pharmaceutically acceptable salt or solvate thereof, or a solvate of a pharmaceutically acceptable salt thereof.

The compounds of the present invention can be prepared by methods known in the art or analogous to the methods of Examples 3 and 4. It will be appreciated that when adapting methods of the literature or of Examples 3 and 4 that functional groups of intermediate compounds may need to be protected by protecting groups. Functional groups which it is desirable to protect include hydroxy, carboxylate and amino groups. Suitable protecting groups for hydroxy include trialkylsilyl or diarylalkyl-silyl (for example tert-butyldimethylsilyl, tert-butyldiphenylsilyl or trimethylsilyl), tetrahydropyranyl, tert-butyl, methoxymethyl, benzyloxymethyl and 4-methoxybenzyl. Suitable protecting groups for carboxylate include allyl, ethyl, tert-butyl and benzyl esters. Suitable protecting groups for amino include tert-butyloxycarbonyl, 2,4,6-trimethoxybenzyl and benzyloxycarbonyl. The use of protecting groups is described in 'Protective Groups in Organic Synthesis', third edition, T.W. Greene & P.G.M. Wutz, Wiley-Interscience (1999). The protective group may also be a polymer resin such as Wang resin or a 2-chlorotriyl chloride resin.

Alternatively, a compound of formula (I) can be isolated from natural sources using the methodology of Examples 1 or 2.

The compounds of the invention may also be combined and/or co-administered with any antithrombotic agent with a different mechanism of action, such as an
 5 anticoagulant (for example a vitamin K antagonist, an unfractionated or low molecular weight heparin, a synthetic heparin fragment such as fondaparinux, a thrombin inhibitor, a factor Xa inhibitor or other coagulation factor/enzyme inhibitor, a recombinant coagulation factor such as a recombinant human activated protein C) or an antiplatelet agent (such as acetylsalicylic acid, dipyridamole, ticlopidine, clopidogrel or other ADP-receptor [such as
 10 a P2Y₁₂ or P2Y₁] antagonist, a thromboxane receptor and/or synthetase inhibitor, a fibrinogen receptor antagonist, a prostacyclin mimetic or a phosphodiesterase inhibitor).

The compounds of the invention may further be combined and/or coadministered with thrombolytics such as tissue plasminogen activator (natural, recombinant or modified), streptokinase, urokinase, prourokinase, anisoylated plasminogen-streptokinase
 15 activator complex (APSAC), animal salivary gland plasminogen activators, and the like, in the treatment of thrombotic diseases, in particular myocardial infarction, ischaemic stroke and massive pulmonary embolism.

Thus, in a further aspect the present invention provides a combination (combined and/or co-administered) of a compound of formula (I), wherein X is (CH₂)_mY(CH₂)_n; m
 20 and n are, independently, 1, 2, 3, 4, 5 or 6; provided that m + n is not more than 6; Y is a bond, O, S(O)_p, or S-S; R¹ is CO₂R¹⁵ or a carboxylic acid isostere such as S(O)₂OH, S(O)₂NHR¹⁵, PO(OR¹⁵)OH, PO(OR¹⁵)NH₂, B(OR¹⁵)₂, PO(R¹⁵)OH, PO(R¹⁵)NH₂ or tetrazole; R², R³, R⁴, R⁵ and R⁶ are, independently, hydrogen, C₁₋₆ alkyl (optionally substituted by halogen, hydroxy, cyano, SH, S(O)₃H, S(O)_q(C₁₋₆ alkyl), OC(O)(C₁₋₄ alkyl),
 25 CF₃, C₁₋₄ alkoxy, OCF₃, COOH, CONH₂, CONH(C₁₋₆ alkyl), NH₂, CNH(NH₂), or NHCNH(NH₂)), C₃₋₆ cycloalkyl(C₁₋₄)alkyl (wherein the cycloalkyl ring is optionally substituted by halogen, hydroxy, cyano, C₁₋₄ alkyl, CF₃, C₁₋₄ alkoxy, OCF₃, NH₂, CNH(NH₂) or NHCNH(NH₂)), heterocyclyl(C₁₋₄)alkyl (wherein the heterocyclyl ring is optionally substituted by halogen, hydroxy, cyano, C₁₋₄ alkyl, CF₃, C₁₋₄ alkoxy, OCF₃,
 30 NH₂, CNH(NH₂) or NHCNH(NH₂)), phenyl(C₁₋₄)alkyl (wherein the phenyl ring is optionally substituted by halogen, hydroxy, cyano, C₁₋₄ alkyl, CF₃, C₁₋₄ alkoxy, OCF₃, NH₂, CNH(NH₂) or NHCNH(NH₂)) or heteroaryl(C₁₋₄)alkyl (wherein the heteroaryl ring is

optionally substituted by halogen, hydroxy, cyano, C₁₋₄ alkyl, CF₃, C₁₋₄ alkoxy, OCF₃, NH₂, CNH(NH₂) or NHCNH(NH₂); p and q are, independently, 0, 1 or 2; R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹² and R¹³ are, independently, H or C₁₋₄ alkyl; R¹⁴ is H or C₁₋₄ alkyl; and, R¹⁵ is H or C₁₋₄ alkyl; or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt; and an antithrombotic agent with a different mechanism of action {such as an anticoagulant (for example a vitamin K antagonist, an unfractionated or low molecular weight heparin, a synthetic heparin fragment such as fondaparinux, a thrombin inhibitor, a factor Xa inhibitor or a recombinant coagulation factor such as a recombinant human activated protein C) or an antiplatelet agent (such as acetylsalicylic acid, dipyridamole, ticlopidine, clopidogrel or other ADP-receptor [such as a P2Y₁₂ or P2Y₁] antagonist, a thromboxane receptor and/or synthetase inhibitor, a fibrinogen receptor antagonist, a prostacyclin mimetic or a phosphodiesterase inhibitor)} or a thrombolytic {such as tissue plasminogen activator (natural, recombinant or modified), streptokinase, urokinase, prourokinase, anisoylated plasminogen-streptokinase activator complex (APSAC), animal salivary gland plasminogen activators}.

The compounds of the invention should have a selectivity for carboxypeptidase U over carboxypeptidase N of >50:1, for example >100:1, using the assay described below.

The inhibiting effect of the compounds of the present invention was estimated using the assay described in: Dirk Hendriks, Simon Scharpé and Marc van Sande, *Clinical Chemistry*, 31, 1936-1939 (1985); and Wei Wang, Dirk F. Hendriks, Simon S. Scharpé, *The Journal of Biological Chemistry*, 269, 15937-15944 (1994), using a substrate concentration of 4 mM.

The invention also provides a method of treating a condition where inhibition of carboxypeptidase U is beneficial in a mammal suffering from, or at risk of, said condition, which comprises administering to the mammal a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, as hereinbefore defined.

For the above-mentioned therapeutic uses the dosage administered will vary with the compound employed, the mode of administration, the treatment desired and the disorder indicated.

The compounds of formula (I) and pharmaceutically acceptable salts, solvates or solvates of salts thereof may be used on their own but will generally be administered in the

form of a pharmaceutical composition in which the formula (I) compound, salt, solvate or solvate of salt (active ingredient) is in association with a pharmaceutically acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition will, for example, comprise from 0.05 to 99 %w (per cent by weight), such as from 0.05 to 80 %w, for example from 0.10 to 70 %w, such as from 0.10 to 50 %w, of active ingredient, all percentages by weight being based on total composition.

The present invention thus also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, as hereinbefore defined, in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

The invention further provides a process for the preparation of a pharmaceutical composition of the invention which comprises mixing a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, as hereinbefore defined, with a pharmaceutically acceptable adjuvant, diluent or carrier.

Also included in the invention are derivatives of compounds of formula (I) which have the biological function of compounds of formula (I), such as prodrugs. Prodrugs are, for example, methyl, (pivaloyloxy)methyl esters and [(ethoxycarbonyl)oxy]methyl esters of carboxylic acids.

The following Examples illustrate the invention.

EXAMPLE 1

This Example describe the isolation of Compounds 1 to 10.

General Experimental Procedures

Water was Milli-Q filtered, while all other solvents used were Omnisolv. A YMC basic C18 5uM, 21.2 mm x 150 mm, column and Hypersil BDS C18 5uM, 21.2 x 150 mm column were used for preparative HPLC. NMR spectra were recorded on a Varian Inova 600 or 500 MHz NMR spectrometer. Samples were dissolved in d₆-DMSO and chemical shifts were calculated relative to the solvent peak (DMSO ¹H δ 2.49 and ¹³C 39.5 ppm). Mass spectra were measured on a Fisons VG Platform II, using positive electrospray ionisation mode. The elution solvent was a mixture acetonitrile/water 50% at 0.1 ml/min.

Animal Material

The sponge (*Melophlus* sp.) was collected by SCUBA diving off Ribbon Reef No. 5, Australia and a voucher sample (G319104) is lodged at the Queensland Museum, Brisbane, Australia.

Extraction and Isolation

A freeze dried ground sample of the sponge *Melophlus* sp (128g) collected from Ribbon Reef No. 5 in far North Queensland, Australia was exhaustively extracted with methanol (2 l). The solvent was evaporated to yield a dark brown residue (28g). The residue was redissolved in a mixture of EtOAc (20 mL) and water (60 mL) and separated by droplet countercurrent chromatography with water as the stationary phase and a gradient from EtOAc to butanol as the mobile phase at 5 mL/min. Two minute fractions were collected and every second fraction analysed by electrospray mass spectrometry. Like fractions were combined yielding 5 fractions. Fraction 2 (320 mg) was separated by centrifugal partition chromatography (Sanki CPC, ascending mode) using a trisolvent mixture $\text{CHCl}_3/\text{MeOH}/\text{H}_2\text{O}$ (7:13:8) with the lower phase as stationary phase. A flow rate of 2mL/min was used and two minute fractions were collected for 360 min. Every second fraction was analyzed by positive electrospray mass spectrometry and like fractions combined. Fractions 91-101 were combined to yield impure Compound 2 (10.8 mg) and fractions 107-120 were combined to yield impure Compound 1 (12.4 mg). The impure peptide fractions of Compounds 1 and 2 were each partitioned between aqueous TFA (1%) and hexane. The aqueous layers from each partition contained pure Compound 2 (9.5 mg) and Compound 1 (11.5 mg). Fractions 1, 3 and 4 from the original DCCC separation were combined with the remaining fractions from the CPC separation and preabsorbed onto C18 (3g). The preabsorbed fractions were further separated by C18 HPLC hypersil BDS C18 (5uM, 20mm x 150 mm) using a water/methanol gradient from water containing 1% TFA to methanol containing 1% TFA at 10 mL/min over 60 min. One minute fractions were collected and all fractions analyzed by electrospray mass spectrometry. Like fractions were combined. Fractions 51-58 contained peptides related to Compounds 1 and 2, and were combined (fraction A; 65 mg). This peptide fraction A was further purified by RP HPLC on YMC basic C18 5 uM, 20 mm x 150 mm elution with 65 % water (containing 1% TFA) and 35% MeCN (containing 1% TFA) at a flow rate of 10 mL/min. Twelve second

fractions were collected for 36 minutes. Fractions 58-60 was pure Compound 2 (11 mg), fractions 67-69 was pure Compound 1 (11 mg), fractions 70-72 was pure Compound 3 (2 mg), fractions 73-77 was pure Compound 7 (11.2 mg), fractions 79-82 was pure Compound 4 (7.29 mg), fractions 91-96 was pure Compound 8 (8.75 mg), fractions 101-106 was pure Compound 9 (6.02 mg), fractions 118-125 was pure Compound 5 (2.08 mg), fractions 128-138 was pure Compound 10 (5.73 mg) and fractions 140-150 was pure Compound 6 (5.94 mg).

Compound 1: MS: (positive ESI) $[M+H]^+$ m/z 826. 1H and ^{13}C NMR (d_6 -DMSO): see Table 1.

Compound 2: MS: (positive ESI) $[M+H]^+$ m/z 876, 878. 1H and ^{13}C NMR (d_6 -DMSO): see Table 2.

Compound 3: MS: (positive ESI) $[M+H]^+$ m/z 890, 892. 1H and ^{13}C NMR (d_6 -DMSO): see Table 3.

Compound 4: MS: (positive ESI) $[M+H]^+$ m/z 840. 1H and ^{13}C NMR (d_6 -DMSO): see Table 4.

Compound 5: MS: (positive ESI) $[M+H]^+$ m/z 860, 862. 1H and ^{13}C NMR (d_6 -DMSO): see Table 5.

Compound 6: MS: (positive ESI) $[M+H]^+$ m/z 861, 863. 1H and ^{13}C NMR (d_6 -DMSO): see Table 6.

Compound 7: MS: (positive ESI) $[M+H]^+$ m/z 895, 897. 1H and ^{13}C NMR (d_6 -DMSO): see Table 7.

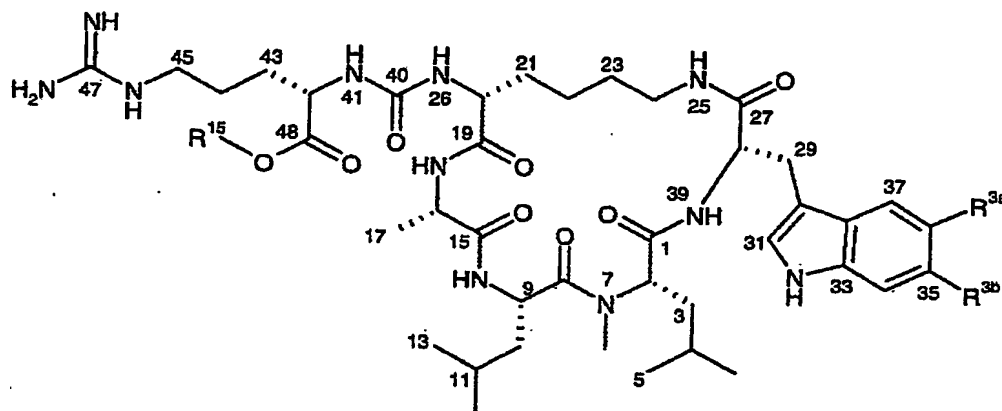
Compound 8: MS: (positive ESI) $[M+H]^+$ m/z 909, 911. 1H and ^{13}C NMR (d_6 -DMSO): see Table 8.

Compound 9: MS: (positive ESI) $[M+H]^+$ m/z 909, 911. 1H and ^{13}C NMR (d_6 -DMSO): see Table 9.

Compound 10: MS: (positive ESI) $[M+H]^+$ m/z 973, 975, 977. 1H and ^{13}C NMR (d_6 -DMSO): see Table 10.

After extensive studies including ^1H , gHSQC, gHMBC, and gCOSY experiments, Compounds 1-10 were identified as cyclic peptides. The absolute stereochemistry of Compound 1 was confirmed by single crystal X-ray diffraction analysis.

Compounds 1-5



R^{3a}	R^{3b}	R^{15}	
H	H	H	Compound 1
OH	Cl	H	Compound 2
OH	Cl	CH_3	Compound 3
H	H	CH_3	Compound 4
H	Cl	H	Compound 5

Table 1 ^1H (600 MHz), ^{13}C (125 MHz), HMBC and COSY
NMR data for Compound 1 in d_6 -DMSO

Atom No	^{13}C (mult) ^a	^1H (mult, J Hz)	^{13}C correlations	COSY
N-Methyl leucine				
1	169.3 (s)	-	-	-
2	58.2 (d)	4.72 (dd, 5.9, 8.8 Hz, 1H)	1, 3, 4, 7-NMe, 8	H3a, H3b
3	36.6 (t)	1.22 (m, 1H)	1, 2, 5, 6	H2, H3b, H4
		1.63 (m, 1H)	2, 4, 5, 6	H2, H3a, H4
4	24.3 (d)	1.34 (m, 1H)	2, 3, 5, 6	H3a, H3b, H5, H6
5	22.2 (q)	0.85 (d, 6.8 Hz, 3H)	3, 4, 6	H4
6	23.1 (q)	0.82 (d, 6.8 Hz, 3H)	3, 4, 5	H4
NMe	27.6 (q)	1.81 (s, 3H)	2, 8	-
Leucine				

8	172.8 (s)	-	-	-
9	45.7 (d)	4.77 (ddd, 2.9, 4.9, 9.8 Hz, 1H)	10, 11, 8	H10a, H10b, H14
10	39.8 (t)	1.66 (m, 1H) 1.17 (m, 1H)	-	H9, H10b, H11
11	24.7 (d)	1.82 (m, 1H)	10	H9, H10a, H11
12	21.6 (q)	0.87 (d, 6.8 Hz, 3H)	10, 11, 13	H10a, H10b, H12, H13
13	22.9 (q)	0.91 (d, 6.8 Hz, 3H)	10, 11, 12	H11
14	-	8.73 (d, 4.9 Hz, 1H)	10, 15, 16	H11
alanine				H9
15	174.1 (s)	-	-	-
16	47.9 (d)	4.20 (dq, 7.8, 7.8 Hz, 1H)	15, 17	H17, H18
17	16.7 (q)	1.30 (d, 7.8 Hz, 3H)	15, 16	H16
18	-	7.20 (d, 4.9 Hz, 1H)	19, 20, 16, 17	H16
lysine				
19	172.7 (s)	-	-	-
20	54.6 (d)	3.92 (ddd, 5.9, 6.8, 6.8 Hz, 1H)	19, 21, 22, 40	H21, H26
21	32.5 (t)	1.65 (m, 2H)	-	H20, H22a, H22b
22	20.3 (t)	1.40 (m, 1H) 1.10 (m, 1H)	-	H21, H22b, H23
23	28.3 (t)	1.40 (m, 2H)	-	H21, H22a, H23
24	38.0 (t)	2.75 (m, 1H) 3.58 (m, 1H)	27	H22a, H22b, H24a, H24b
25	-	7.44 (dd, 1.2, 7.8 Hz, 1H)	22, 23	H23, H24b, H25
26	-	6.45 (d, 6.8 Hz, 1H)	27	H23, H24a, H25
tryptophan			39, 20, 21	H24a, H24b
27	171.4 (s)	-	-	H20
28	53.9 (d)	4.40 (ddd, 2.9, 8.8, 11.7 Hz, 1H)	1, 27, 30	H29a, H29b, H39
29	27.9 (t)	2.88 (dd, 11.7, 13.7 Hz, 1H) 3.35 (dd, 2.9, 13.7 Hz, 1H)	28, 27, 30, 31, 38	H28, H29b
30	110.4 (s)	-	28, 27, 30, 31, 38	H28, H29a
31	124.0 (d)	6.68 (bs, 1H)	-	-
32	-	10.80 (bs, 1H)	29, 30, 33, 38	H32
33	136.5 (s)	-	30, 31, 33, 38	H31
34	111.5 (d)	7.24 (d, 7.8 Hz, 1H)	-	-
35	121.0 (d)	7.00 (dd, 7.8, 7.8 Hz, 1H)	36, 38	H35, H36
36	118.5 (d)	6.92 (dd, 7.8, 7.8 Hz, 1H)	33, 37	H34, H36
37	116.9 (d)	7.20 (d, 7.8 Hz, 1H)	34, 38	H35, H37
			35, 33	H36, H35

38	127.0 (s)	-	-	-
39		8.62 (d, 8.8 Hz, 1H)	1, 28, 29	H28
40	157.5 (s)	-	-	-
arginine				
41	-	6.42 (d, 7.8 Hz, 1H)	43, 42, 48, 40	H42
42	52.9 (d)	4.05 (ddd, 5.9, 7.8, 7.8 Hz, 1H)	41, 43, 44, 48	H41, H43a, H43b
43	29.1 (t)	1.52 (m, 1H)	-	H42, H44, H43b
		1.69 (m, 1H)	-	H42, H43a, H44
44	25.1 (t)	1.40 (m, 2H)	-	H43a, H43b, H45
45	40.0 (t)	3.06 (dt, 5.9, 5.9 Hz, 2H)	43, 44, 47	H45, H46
46	-	7.64 (t, 5.9 Hz, 1H)	45, 47	H45
47	156.9 (s)	-	-	-
48	175.1 (s)	-	-	-

^aChemical shifts determined from 2D heteronuclear experiments

Table 2 ¹H (600 MHz), ¹³C (125 MHz), HMBC and COSY
NMR data for Compound 2 in *d*₆-DMSO

Atom No	¹³ C (mult) ^a	¹ H (mult, J Hz)	²³ J _{CH} correlations	COSY
N-Methyl leucine				
1	169.4 (s)	-	-	-
2	58.4 (d)	4.72 (dd, 5.9, 7.8 Hz, 1H)	1, 3, 4, 8, 7-NMe	H3a, H3b
3	36.5 (t)	1.22 (m, 1H)	2, 4, 5, 6	H2, H3b, H4
		1.63 (m, 1H)	2, 4, 5, 6	H2, H3a, H4
4	23.8 (d)	1.32 (m, 1H)	2, 3, 5, 6	H3a, H3b, H5, H6
5	22.1 (q)	0.86 (d, 6.8 Hz, 3H)	3, 4, 6	H4
6	22.8 (q)	0.83 (d, 6.8 Hz, 3H)	3, 4, 5	H4
NMe	27.7 (q)	1.80 (s, 3H)	2, 8	-
Leucine				
8	172.9 (s)	-	-	-
9	47.8 (d)	4.77 (ddd, 2.9, 4.9, 9.8 Hz, 1H)	-	H10a, H10b, H14
10	39.9 (t)	1.66 (m, 1H)	-	H9, H10b, H11
		1.17 (m, 1H)	-	H9, H10a, H11
11	23.4 (d)	1.82 (m, 1H)	-	H10a, H10b, H12, H13
12	22.5 (q)	0.88 (d, 6.8 Hz, 3H)	10, 11, 13	H11
13	23.0 (q)	0.93 (d, 6.8 Hz, 3H)	10, 11, 12	H11
14	-	8.74 (d, 5.9 Hz, 1H)	9, 10, 15	H9
alanine				

15	174.0 (s)	-	-	-
16	48.0 (d)	4.17 (dq, 3.8, 6.8 Hz, 1H)	15, 17	H17, H18
17	16.8 (q)	1.29 (d, 6.8 Hz, 3H)	15, 16	H16
18		7.16 (d, 3.9 Hz, 1H)	19, 16, 17	H16
lysine				
19	172.5 (s)	-	-	-
20	53.9 (d)	3.92 (ddd, 5.9, 6.8, 6.8 Hz, 1H)	19, 21, 22, 40	H21, H26
21	32.9 (t)	1.57 (m, 2H)	-	H20, H22a, H22b
22	20.1 (t)	1.40 (m, 1H)	-	H21, H22b, H23
		1.10 (m, 1H)	-	H21, H22a, H23
23	28.1 (t)	1.40 (m, 2H)	-	H22a, H22b, H24a, H24b
24	37.0 (t)	2.75 (m, 1H)	-	H23, H24b, H25
		3.56 (m, 1H)	-	H23, H24a, H25
25	-	7.45 (dd, 1.2, 6.8 Hz, 1H)	27, 19	H24a, H24b
26	-	6.45 (d, 6.8 Hz, 1H)	-	H20
tryptophan				
27	170.6 (s)	-	-	-
28	53.7 (d)	4.38 (ddd, 2.9, 8.8, 12.7 Hz, 1H)	-	H29a, H29b, H39
29	27.9 (t)	2.83 (dd, 12.7, 12.7 Hz, 1H)	28, 27, 30, 31, 38	H28, H29b
		3.31 (dd, 2.9, 12.7 Hz, 1H)	28, 27, 30, 31, 38	H28, H29a
30	109.3 (s)	-	-	-
31	124.1 (d)	6.60 (bs, 1H)	29, 30, 33, 38	H32
32	-	10.60 (bs, 1H)	30, 31, 33, 38	H31
33	131.1 (s)	-	-	-
34	111.1 (d)	7.20 (s, 1H)	35, 36, 38	-
35	115.0 (s)	-	-	-
36	145.9 (s)	-	-	-
37	102.1 (d)	7.01 (s, 1H)	30, 35, 33, 36	-
38	126.3 (s)	-	-	-
39	-	8.64 (d, 9.8 Hz, 1H)	1	H28
40	157.7 (s)	-	-	-
arginine				
41	-	6.36 (d, 5.6 Hz, 1H)	41, 42, 47	H42
42	52.7 (d)	4.07 (ddd, 5.6, 7.8, 7.8 Hz, 1H)	43, 44, 48	H41, H43a, H43b
43	29.2 (t)	1.52 (m, 1H)	-	H42, H43b, H44
		1.69 (m, 1H)	-	H42, H43a, H44
44	25.3 (t)	1.46 (m, 2H)	-	H43a, H43b, H45
45	40.7 (t)	3.06 (m, 2H)	43, 44, 47	H46, H45
46	-	7.53 (m, 1H)	45, 47	H45
47	157.0 (s)	-	-	-
48	174.5 (s)	-	-	-

^aChemical shifts determined from 2D heteronuclear experiments

Table 3 ¹H (600 MHz), ¹³C (125 MHz), HMBC and COSY
NMR data for Compound 3 in *d*₆-DMSO

Atom No	¹³ C (mult) ^a	¹ H (mult, J Hz)	²³ J _{CH} correlations	COSY
N-Methyl leucine				
1	168.9 (s)	-	-	-
2	57.2 (d)	4.77 (dd, 5.9, 8.8 Hz, 1H)	8	H3a, H3b
3	35.9 (t)	1.20 (m, 1H)	-	H2, H3b, H4
		1.71 (m, 1H)	-	H2, H3a, H4
4	24.2 (d)	1.35 (m, 1H)	-	H3a, H3b, H5, H6
5	23.0 (q)	0.85 (d, 6.8 Hz, 3H)	3, 4, 6	H4
6	23.3 (q)	0.88 (d, 6.8 Hz, 3H)	3, 4, 5	H4
NMe	26.9 (q)	1.87 (s, 3H)	2, 8	-
Leucine				
8	172.2 (s)	-	-	-
9	47.8 (d)	4.79 (ddd, 2.9, 4.9, 9.8 Hz, 1H)	-	H10a, H10b, H14
10	39.4 (t)	1.70 (m, 1H)	-	H9, H10b, H11
		1.22 (m, 1H)	-	H9, H10a, H11
11	24.1 (d)	1.84 (m, 1H)	-	H10a, H10b, H12, H13
12	21.5 (q)	0.90 (d, 6.8 Hz, 3H)	10, 11, 13	H11
13	23.0 (q)	0.95 (d, 6.8 Hz, 3H)	10, 11, 12	H11
14	-	8.76 (d, 4.9 Hz, 1H)	15	H9
alanine				
15	173.6 (s)	-	-	-
16	47.5 (d)	4.19 (dq, 5.8, 6.8 Hz, 1H)	-	H17, H18
17	16.5 (q)	1.32 (d, 6.8 Hz, 3H)	15, 16	H16
18	-	7.22 (d, 5.9 Hz, 1H)	19	H16
lysine				
19	171.9 (s)	-	-	-
20	54.2 (d)	3.94 (ddd, 5.9, 6.8, 6.8 Hz, 1H)	19, 21, 22	H21, H26
21	31.7 (t)	1.60 (m, 2H)	-	H20, H22a, H22b
22	20.1 (t)	1.40 (m, 1H)	-	H21, H22b, H23
		1.10 (m, 1H)	-	H21, H22a, H23
23	27.2 (t)	1.40 (m, 2H)	-	H22a, H22b, H24a, H24b
24	38.1 (t)	2.78 (m, 1H)	27	H23, H24b, H25
		3.60 (m, 1H)	-	H23, H24a, H25
25	-	7.42 (dd, 1.2, 7.8 Hz, 1H)	27	H24a, H24b

26	-	6.31 (d, 6.8 Hz, 1H)	40	H20
tryptophan				
27	172.8 (s)	-	-	-
28	53.7 (d)	4.39 (ddd, 2.9, 8.8, 11.7 Hz, 1H)	-	H29a, H29b, H39
29	27.9 (t)	2.86 (dd, 11.7, 13.7 Hz, 1H)	28, 27, 30, 31, 38	H28, H29b
		3.27 (dd, 2.9, 13.7 Hz, 1H)	28, 27, 30, 31, 38	H28, H29a
30	109.4 (s)	-	-	-
31	124.5 (d)	6.62 (bs, 1H)	29, 30, 33, 38	H32
32	-	10.65 (bs, 1H)	30, 31, 33, 38	H31
33	130.4 (s)	-	-	-
34	111.2 (d)	7.22 (s, 1H)	36, 38	-
35	115.3 (s)	-	-	-
36	145.6 (s)	-	-	-
37	102.5 (d)	7.00 (s, 1H)	30, 35, 33	-
38	125.9 (s)	-	-	-
39	-	8.67 (d, 8.8 Hz, 1H)	-	H28
40	157.2 (s)	-	-	-
arginine				
41	-	6.50 (d, 7.8 Hz, 1H)	40	H42
42	51.9 (d)	4.05 (ddd, 5.9, 7.8, 7.8 Hz, 1H)	47	H41, H43a, H43b
43	28.7 (t)	1.56 (m, 1H)	-	H42, H43b, H44
		1.74 (m, 1H)	-	H42, H43a, H44
44	24.9 (t)	1.46 (m, 2H)	-	H43a, H43b, H45
45	39.7 (t)	3.09 (dt, 5.9, 5.9 Hz, 2H)	47	H46, H45
46	-	7.42 (t, 5.9 Hz, 1H)	47	H45
47	156.4 (s)	-	-	-
48	173.1 (s)	-	-	-
48-Me	51.8 (q)	3.62 (s, 3H)	48	-

^aChemical shifts determined from 2D heteronuclear experiments

Table 4 ¹H (600 MHz), ¹³C (125 MHz), and COSY
NMR data for Compound 4 in *d*₆-DMSO

Atom No	¹³ C (mult) ^a	¹ H (mult, J Hz)	COSY
N-Methyl leucine			
1	n.o.	-	-
2	57.9 (d)	4.78 (dd, 5.9, 8.8 Hz, 1H)	H3a, H3b
3	36.1 (t)	1.27 (m, 1H)	H2, H3b, H4
		1.68 (m, 1H)	H2, H3a, H4
4	24.1 (d)	1.37 (m, 1H)	H3a, H3b, H5, H6
5	23.7 (q)	0.79 (d, 6.8 Hz, 3H)	H4

6	20.9 (q)	0.83 (d, 6.8 Hz, 3H)	H4
NMe	27.3 (q)	1.81 (s, 3H)	-
Leucine			
8	n.o.	-	-
9	47.0 (d)	4.78 (ddd, 2.9, 4.9, 9.8 Hz, 1H)	H10a, H10b, H14
10	40.0 (t)	1.63 (m, 1H)	H9, H10b, H11
		1.25 (m, 1H)	H9, H10a, H11
11	24.2 (d)	1.83 (m, 1H)	H10a, H10b, H12, H13
12	20.7 (q)	0.84 (d, 6.8 Hz, 3H)	H11
13	23.9 (q)	0.91 (d, 6.8 Hz, 1H)	H11
14	-	8.79 (d, 4.9 Hz, 1H)	H9
alanine			
15	n.o.	-	-
16	47.3 (d)	4.19 (dq, 7.8, 7.8 Hz, 1H)	H17, H18
17	16.2 (q)	1.33 (d, 7.8 Hz, 3H)	H16
18	-	7.29 (d, 4.9 Hz, 1H)	H16
lysine			
19	n.o.	-	-
20	54.3 (d)	3.87 (ddd, 5.9, 6.8, 6.8 Hz, 1H)	H21, H26
21	32.1 (t)	1.60 (m, 2H)	H20, H22a, H22b
22	21.1 (t)	1.40 (m, 1H)	H21, H22b, H23
		1.10 (m, 1H)	H21, H22a, H23
23	28.1 (t)	1.40 (m, 2H)	H22a, H22b, H24a, H24b
24	38.1 (t)	2.75 (m, 1H)	H23, H24b, H25
		3.59 (m, 1H)	H23, H24a, H25
25	-	7.41 (dd, 1.2, 7.8 Hz, 1H)	H24a, H24b
26	-	6.39 (d, 6.8 Hz, 1H)	H20
tryptophan			
27	n.o.	-	-
28	53.8 (d)	4.38 (ddd, 2.9, 8.8, 11.7 Hz, 1H)	H29a, H29b, H39
29	27.6 (t)	2.81 (dd, 11.7, 13.7 Hz, 1H)	H28, H29b
		3.37 (dd, 2.9, 13.7 Hz, 1H)	H28, H29a
30	n.o.	-	-
31	124.5 (d)	6.72 (bs, 1H)	H32
32	-	10.80 (bs, 1H)	H31
33	n.o.	-	-
34	111.2 (d)	7.37 (d, 7.8 Hz, 1H)	H35
35	120.2 (d)	6.89 (dd, 7.8, 7.8 Hz, 1H)	H34, H36
36	121.0 (d)	7.00 (dd, 7.8, 7.8 Hz, 1H)	H35, H37
37	117.8 (d)	7.21 (d, 7.8 Hz, 1H)	H36, H35

38	n.o.	-	-
39	-	8.64 (d, 8.8 Hz, 1H)	H28
40	n.o.	-	-
arginine			
41	-	6.49 (d, 7.8 Hz, 1H)	H42
42	52.2 (d)	4.19 (ddd, 5.9, 7.8, 7.8 Hz, 1H)	H41, H43a, H43b
43	28.0 (t)	1.52 (m, 1H)	H42, H43b, H44
		1.71 (m, 1H)	H42, H43a, H44
44	24.7 (t)	1.40 (m, 2H)	H43a, H43b, H45
45	40.1 (t)	3.07 (dt, 5.9, 5.9 Hz, 2H)	H46, H45
46	-	7.42 (t, 5.9 Hz, 1H)	H45
47	n.o.	-	-
48	n.o.	-	-
48-Me	52.1 (q)	3.58 (s, 3H)	-

^aChemical shifts determined from 2D heteronuclear experiments

n.o. = not observed

Table 5 ¹H (600 MHz), ¹³C (125 MHz), HMBC and COSY

5

NMR data for Compound 5 in *d*₆-DMSO

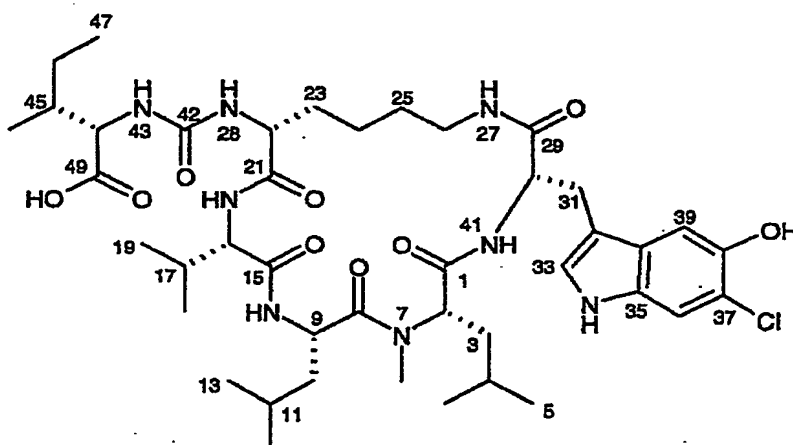
Atom No	¹³ C (mult) ^a	¹ H (mult, <i>J</i> Hz)	²³ J _{CH} correlations	COSY
N-Methyl leucine				
1	168.9 (s)	-	-	-
2	57.5 (d)	4.76 (dd, 5.9, 8.8 Hz, 1H)	1, 3, 8, 7-NMe	H3a, H3b
3	36.6 (t)	1.27 (m, 1H)	-	H2, H3b, H4
		1.65 (m, 1H)	-	H2, H3a, H4
4	24.4 (d)	1.34 (m, 1H)	-	H3a, H3b, H5, H6
5	23.7 (q)	0.82 (d, 6.8 Hz, 3H)	3, 4, 6	H4
6	21.2 (q)	0.84 (d, 6.8 Hz, 3H)	3, 4, 5	H4
NMe	27.5 (q)	1.77 (s, 3H)	2, 8	-
Leucine				
8	172.6 (s)	-	-	-
9	46.8 (d)	4.77 (ddd, 2.9, 4.9, 9.8 Hz, 1H)	-	H10a, H10b, H14
10	40.0 (t)	1.68 (m, 1H)	9, 11	H9, H10b, H11
		1.22 (m, 1H)	-	H9, H10a, H11
11	24.5 (d)	1.82 (m, 1H)	-	H10a, H10b, H12, H13
12	21.4 (q)	0.86 (d, 6.8 Hz, 3H)	10, 11, 13	H11
13	23.0 (q)	0.90 (d, 6.8 Hz, 3H)	10, 11, 12	H11
14	-	8.77 (d, 4.9 Hz, 1H)	9, 10, 15	H9
alanine				

15	173.8 (s)	-	-	-
16	48.2 (d)	4.16 (dq, 4.9, 7.8 Hz, 1H)	15, 17	H17, H18
17	16.8 (q)	1.27 (d, 7.8 Hz, 3H)	15, 16	H16
18	-	7.18 (d, 4.9 Hz, 1H)	19	H16
lysine				
19	172.3 (s)	-	-	-
20	54.1 (d)	3.91 (ddd, 5.9, 6.8, 6.8 Hz, 1H)	19, 21, 22	H21, H26
21	32.1 (t)	1.60 (m, 2H)	-	H20, H22a, H22b
22	20.6 (t)	1.40 (m, 1H)	-	H21, H22b, H23
		1.10 (m, 1H)	-	H21, H22a, H23
23	27.1 (t)	1.40 (m, 2H)	-	H22a, H22b, H24a, H24b
24	38.1 (t)	2.76 (m, 1H)	-	H23, H24b, H25
		3.53 (m, 1H)	-	H23, H24a, H25
25	-	7.50 (dd, 1.2, 7.8 Hz, 1H)	-	H24a, H24b
26	-	6.36 (d, 6.8 Hz, 1H)	40	H20
tryptophan				
27	173.5 (s)	-	-	-
28	53.8 (d)	4.41 (ddd, 2.9, 9.6, 11.7 Hz, 1H)	-	H29a, H29b, H39
29	27.7 (t)	2.90 (dd, 11.7, 13.7 Hz, 1H)	30, 31, 38	H28, H29b
		3.30 (dd, 2.9, 13.7 Hz, 1H)	30, 31, 38	H28, H29a
30	110.9 (s)	-	-	-
31	124.9 (d)	6.78 (bs, 1H)	29, 30, 33, 38	H32
32	-	11.00 (bs, 1H)	30, 31, 33, 38	H31
33	136.7 (s)	-	-	-
34	111.3 (d)	7.30 (d, 1.8 Hz, 1H)	36, 38	H36
35	125.8 (s)	-	-	-
36	118.7 (d)	6.93 (dd, 7.8, 1.8 Hz, 1H)	38, 34	H34, H37
37	118.3 (d)	7.42 (d, 7.8 Hz, 1H)	35, 33	H36
38	125.5 (s)	-	-	-
39	-	8.64 (d, 9.6 Hz, 1H)	1	H28
40	157.5 (s)	-	-	-
arginine				
41	-	6.37 (d, 7.8 Hz, 1H)	40	H42
42	52.6 (d)	4.05 (ddd, 5.9, 7.8, 7.8 Hz, 1H)	43, 44, 48	H41, H43a, H43b
43	29.5 (t)	1.50 (m, 1H)	-	H42, H43b, H44
		1.67 (m, 1H)	-	H42, H43a, H44
44	25.1 (t)	1.40 (m, 1H)	-	H43a, H43b, H45
		1.19 (m, 1H)	-	-
45	40.5 (t)	3.06 (m, 2H)	47	H44, H46
46	-	7.50 (m, 1H)	-	H45
47	156.8 (s)	-	-	-

48	174.3 (s)	-	-	-
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^aChemical shifts determined from 2D heteronuclear experiments

Compound 6



5 Table 6 ¹H (600 MHz), ¹³C (125 MHz), HMBC and COSY
NMR data for Compound 6 in *d*₆-DMSO

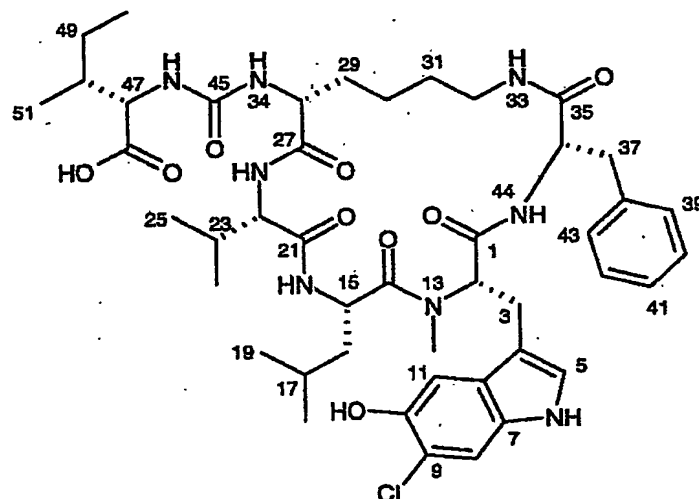
Atom No	¹³ C (mult) ^a	¹ H (mult, <i>J</i> Hz)	¹³ <i>J</i> _{CH} correlations	COSY
N-Methyl leucine				
1	169.4 (s)	-	-	-
2	58.0 (d)	4.72 (dd, 5.9, 8.8 Hz, 1H)	1, 3, 4, 8, 7-NMe	H3a, H3b
3	36.2 (t)	1.25 (m, 1H)	1, 2, 4	H2, H3b, H4
		1.60 (m, 1H)	2, 4	H2, H3a, H4
4	23.0 (d)	1.93 (m, 1H)	2, 3	H3a, H3b, H5, H6
5	23.7 (q)	0.82 (d, 6.8 Hz, 3H)	3, 4, 6	H4
6	24.0 (q)	0.82 (d, 6.8 Hz, 3H)	3, 4, 5	H4
NMe	27.0 (q)	1.90 (s, 3H)	2, 8	-
Leucine				
8	172.5 (s)	-	-	-
9	47.8 (d)	4.70 (ddd, 2.9, 4.9, 9.8 Hz, 1H)	-	H10a, H10b, H14
10	39.2 (t)	1.70 (m, 1H)	-	H9, H10b, H11
		1.22 (m, 1H)	-	H9, H10a, H11
11	27.0 (d)	1.82 (m, 1H)	-	H10a, H10b, H12, H13
12	21.0 (q)	0.84 (d, 6.8 Hz, 3H)	10, 11, 13	H11
13	24.9 (q)	0.96 (d, 6.8 Hz, 3H)	10, 11, 12	H11
14	-	8.69 (d, 4.9 Hz, 1H)	9, 10, 15	H9
valine				

15	172.7 (s)	-	-	-
16	57.8 (d)	3.92 (dd, 5.8, 7.8 Hz, 1H)	-	H17, H20
17	29.7 (d)	1.95 (m, 1H)	16, 18, 19	H16, H18, H19
18	19.4 (q)	0.85 (d, 7.8 Hz, 3H)	16, 17, 19	H17
19	19.0 (q)	1.05 (d, 7.8 Hz, 3H)	16, 17, 18	H17
20	-	6.80 (d, 5.9 Hz, 1H)	16, 17, 19	H16
lysine				
21	172.5 (s)	-	-	-
22	54.8 (d)	3.91 (ddd, 5.9, 6.8, 6.8 Hz, 1H)	19, 21, 22, 42	H23, H28
23	31.5 (t)	1.60 (m, 2H)	-	H22, H24a, H24b
24	20.1 (t)	1.40 (m, 1H)	-	H23, H24b, H25
		1.10 (m, 1H)	-	H23, H24a, H25
25	28.1 (t)	1.40 (m, 2H)	-	H24a, H24b, H26a, H26b
26	38.1 (t)	2.80 (m, 1H)	27	H25, H26b, H27
		3.61 (m, 1H)	-	H25, H26a, H27
27	-	7.40 (dd, 1.2, 7.8 Hz, 1H)	27	H26a, H26b
28	-	6.47 (d, 5.9 Hz, 1H)	42, 22, 23	H22
tryptophan				
29	171.6 (s)	-	-	-
30	53.2 (d)	4.41 (ddd, 2.9, 8.8, 11.7 Hz, 1H)	-	H31a, H31b, H41
31	27.9 (t)	2.90 (dd, 11.7, 13.7 Hz, 1H)	29, 33, 32, 30	H30, H31b
		3.40 (dd, 2.9, 13.7 Hz, 1H)	30, 32, 33	H30, H31a
32	109.5 (s)	-	-	-
33	125.5 (d)	6.65 (bs, 1H)	29, 30, 35, 40	H34
34	-	10.64 (bs, 1H)	32, 33, 35, 40	H33
35	130.4 (s)	-	-	-
36	111.1 (d)	7.20 (s, 1H)	33, 37, 38, 40	-
37	115.0 (s)	-	-	-
38	146.3 (s)	-	-	-
39	102.3 (d)	7.00 (s, 1H)	35, 33, 32, 37, 38	-
40	126.0 (s)	-	-	-
41	-	8.77 (d, 8.8 Hz, 1H)	1	H30
42	157.6 (s)	-	-	-
isoleucine				
43	-	6.35 (d, 7.8 Hz, 1H)	42	H44
44	56.9 (d)	4.06 (dd, 5.9, 7.8 Hz, 1H)	42, 45, 46, 48, 49	H43, H45
45	36.8 (d)	1.70 (m, 1H)	-	H44, H46b, H46a, H48
46	24.7 (t)	1.40 (m, 1H)	44, 47, 48	H46b, H47, H45
		1.15 (m, 1H)	44, 47, 48	H47, H45, H46a
47	11.7 (q)	0.82 (t, 6.8 Hz, 3H)	45, 46	H46a, H46b

48	15.4 (q)	0.84 (d, 6.8 Hz, 3H)	44, 45, 46	H45
49	173.7 (s)	-	-	-

^aChemical shifts determined from 2D heteronuclear experiments

Compound 7



5 **Table 7** ¹H (600 MHz), ¹³C (125 MHz), HMBC and COSY
NMR data for Compound 7 in *d*₆-DMSO

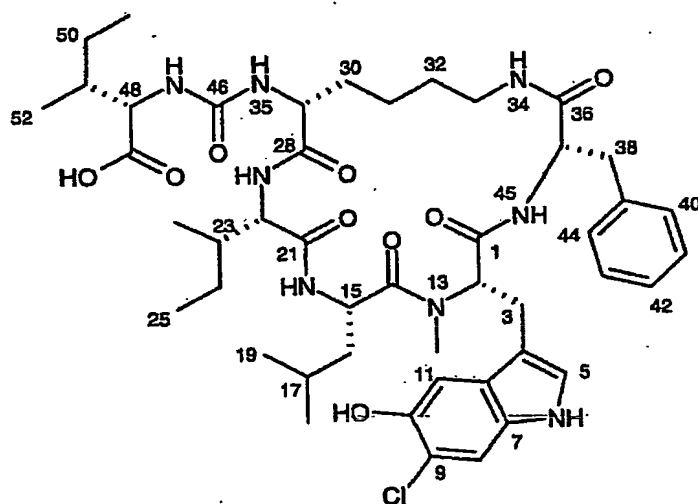
Atom No	¹³ C (mult) ^a	¹ H (mult, J Hz)	¹³ J _{CH} correlations	COSY
N-Methyl tryptophan				
1	169.8 (s)	-	-	-
2	61.0 (d)	4.66 (dd, 2.6, 10.4 Hz, 1H)	1, 3, 4, 14, 13-NMe	H3a, H3b
3	22.3 (t)	2.73 (m, 1H)	1, 5, 4, 2, 12	H2, H3b
		3.07 (m, 1H)	2, 4, 5, 12	H2, H3a
4	108.9 (s)	-	-	-
5	124.3 (d)	6.87 (bs, 1H)	3, 4, 7, 12	H6
6	-	10.66 (bs, 1H)	4, 5, 7, 12	H5
7	130.7 (s)	-	-	-
8	111.8 (d)	7.26 (s, 1H)	7, 9, 10, 12	-
9	115.8 (s)	-	-	-
10	145.8 (s)	-	-	-
11	102.7 (d)	6.98 (s, 1H)	4, 7, 9, 10, 12	-
12	126.8 (s)	-	-	-
NMe	27.5 (q)	1.91 (s, 3H)	2, 14	-
Leucine				

14	172.5 (s)	-	-	-
15	46.9 (d)	4.21 (ddd, 2.9, 4.9, 9.8 Hz, 1H)	16, 21	H16a, H16b, H20
16	36.9 (t)	-0.50 (dd, 11.7, 11.7 Hz, 1H)	14, 17, 18	H15, H16b, H17
		0.90 (m, 1H)	-	H15, H16a, H17
17	24.8 (d)	1.40 (m, 1H)	-	H16a, H16b, H18, H19
18	19.7 (q)	0.26 (d, 6.8 Hz, 3H)	16, 17, 19	H17
19	22.0 (q)	0.40 (d, 6.8 Hz, 3H)	16, 17, 18	H17
20	-	8.42 (d, 4.3 Hz, 1H)	15, 16, 21	H15
valine				
21	172.2 (s)	-	-	-
22	57.6 (d)	3.79 (dd, 6.9, 7.8 Hz, 1H)	23, 24, 25	H23, H26
23	30.0 (d)	1.90 (m, 1H)	22, 24, 25	H22, H24, H25
24	18.9 (q)	0.86 (d, 7.8 Hz, 3H)	22, 23, 25	H23
25	18.8 (q)	0.93 (d, 7.8 Hz, 3H)	22, 23, 24	H23
26	-	6.74 (d, 6.9 Hz, 1H)	22, 23, 27	H22
lysine				
27	171.9 (s)	-	-	-
28	53.8 (d)	3.86 (ddd, 5.9, 6.9, 6.8 Hz, 1H)	27, 29, 30, 45	H29, H34
29	31.3 (t)	1.54 (m, 2H)	-	H28, H34
30	20.2 (t)	1.40 (m, 1H)	-	H29, H30b, H31
		1.10 (m, 1H)	-	H29, H30a, H31
31	28.2 (t)	1.40 (m, 2H)	-	H30a, H30b, H32a, H32b
32	37.9 (t)	2.86 (m, 1H)	35	H31, H32b, H33
		3.58 (m, 1H)	30, 31, 35	H31, H32a, H33
33	-	7.40 (dd, 1.2, 7.8 Hz, 1H)	32, 35	H32a, H32b
34	-	6.43 (d, 6.9 Hz, 1H)	27, 29, 45	H28
phenylalanine				
35	171.0 (s)	-	-	-
36	54.8 (d)	4.57 (ddd, 2.9, 9.5, 11.7 Hz, 1H)	1, 35, 37	H37a, H37b, H44
37	37.9 (t)	2.75 (dd, 11.7, 13.7 Hz, 1H)	35, 36, 38, 39, 43	H36, H37b
		3.40 (dd, 2.9, 13.7 Hz, 1H)	36, 38, 39, 43	H36, H37a
38	138.6 (s)	-	-	-
39	128.9 (d)	7.07 (d, 7.8 Hz, 1H)	37, 38, 41, 43	H40, H41
40	127.9 (d)	7.22 (dd, 7.8, 7.8 Hz, 1H)	38, 42	H39, H41
41	126.2 (d)	7.15 (t, 7.8 Hz, 1H)	39, 43	H40, H42
42	127.9 (d)	7.22 (dd, 7.8, 7.8 Hz, 1H)	38, 40	H41, H43
43	128.29 (d)	7.07 (d, 7.8 Hz, 1H)	37, 38, 39, 41	H42
44	-	8.76 (d, 9.5 Hz, 1H)	1, 36, 37	H36
45	157.3 (s)	-	-	-
isoleucine				

46	-	6.28 (d, 8.7 Hz, 1H)	45, 47, 52	H47
47	56.6 (d)	4.04 (dd, 5.9, 7.8, 7.8 Hz, 1H)	45, 48, 49, 51, 52	H46, H48
48	36.9 (d)	1.71 (m, 1H)	47, 49, 50, 51	H47, H49b, H51
49	24.5 (t)	1.35 (m, 1H)	47, 48, 50, 51	H48, H49b, H50
		1.10 (m, 1H)	47, 48, 50, 51	H48, H49a, H50
50	11.1 (q)	0.83 (t, 6.8 Hz, 3H)	48, 49	H49a, H49b
51	15.6 (q)	0.82 (d, 6.8 Hz, 3H)	47, 48, 49	H48
52	173.8 (s)	-	-	-

^aChemical shifts determined from 2D heteronuclear experiments

Compound 8



5 Table 8 ¹H (600 MHz), ¹³C (125 MHz) and COSY
NMR data for Compound 8 in *d*₆-DMSO

Atom No	¹³ C (mult) ^a	¹ H (mult, J Hz)	COSY
N-Methyl tryptophan			
1	n.o.	-	-
2	60.8 (d)	4.65 (dd, 2.6, 9.9 Hz, 1H)	H3a, H3b
3	21.9 (t)	2.73 (m, 1H)	H2, H3b
	-	3.08 (m, 1H)	H2, H3a
4	n.o.	-	-
5	124.7 (d)	6.87 (d, 1.9 Hz, 1H)	H6
6		10.66 (bs, 1H)	H5
7	n.o.	-	-
8	111.5 (d)	7.23 (s, 1H)	-

9	n.o.	-	-
10	n.o.	-	-
11	103.4 (d)	6.94 (s, 1H)	-
12	n.o.	-	-
NMe	27.4 (q)	1.90 (s, 3H)	-
Leucine			
14	n.o.	-	-
15	47.4 (d)	4.18 (ddd, 2.9, 4.9, 9.8 Hz, 1H)	H16a, H16b, H20
16	37.0 (t)	-0.50 (dd, 9.8, 9.8 Hz, 1H)	H15, H16b, H17
		0.91 (m, 1H)	H15, H16a, H17
17	24.9 (d)	1.40 (m, 1H)	H16a, H16b, H19, H18
18	19.5 (q)	0.22 (d, 6.8 Hz, 3H)	H17
19	22.3 (q)	0.36 (d, 6.8 Hz, 3H)	H17
20	-	8.40 (d, 4.8 Hz, 1H)	H15
isoleucine			
21	n.o.	-	-
22	55.8 (d)	3.93 (dd, 7.8, 8.2 Hz, 1H)	H23, H27
23	37.0 (d)	1.72 (m, 1H)	H22, H24a, H24b, H26
24	24.2 (t)	1.08 (m, 1H)	H24b, H23, H25
		1.30 (m, 1H)	H24a, H23, H25
25	12.0 (q)	0.82 (d, 7.0 Hz, 3H)	H24a, H24b
26	15.7 (q)	0.83 (d, 7.0 Hz, 3H)	H23
27	-	6.70 (d, 6.9 Hz, 1H)	H22
lysine			
28	n.o.	-	-
29	54.3 (d)	3.85 (ddd, 5.9, 6.8, 6.8 Hz, 1H)	H30, H35
30	31.8 (t)	1.54 (m, 1H)	H29, H30b, H31a, H31b
		1.72 (m, 1H)	H29, H30a, H31a, H31b
31	24.9 (t)	1.40 (m, 1H)	H32, H31b, H30a, H30b
		1.10 (m, 1H)	H32, H31a, H30a, H30b
32	28.1 (t)	1.40 (m, 2H)	H31a, H31b, H33a, H33b
33	38.0 (t)	2.80 (m, 1H)	H32, H33b, H34
		3.55 (m, 1H)	H32, H33a, H34
34	-	7.43 (dd, 1.2, 8.8 Hz, 1H)	H33a, H33b
35	-	6.45 (d, 6.8 Hz, 1H)	H29
phenylalanine			
36	n.o.	-	-
37	54.5 (d)	4.58 (ddd, 2.9, 8.8, 11.7 Hz, 1H)	H38a, H38b, H45
38	37.4 (t)	2.73 (dd, 11.7, 11.7 Hz, 1H)	H37, H38b
		3.37 (dd, 2.9, 11.7 Hz, 1H)	H37, H38a
39	n.o.	-	-
40	128.3 (d)	7.05 (d, 7.8 Hz, 1H)	H41, H42

41	128.0 (d)	7.19 (dd, 7.8, 7.8 Hz, 1H)	H40, H42
42	125.9 (d)	7.14 (t, 7.8 Hz, 1H)	H41, H43
43	128.0 (d)	7.19 (dd, 7.8, 7.8 Hz, 1H)	H42, H44
44	128.3 (d)	7.05 (d, 7.8 Hz, 1H)	H43, H42
45	-	8.68 (d, 8.8 Hz, 1H)	H37
46	n.o.	-	-
isoleucine			
47	-	6.29 (d, 8.8 Hz, 1H)	H48
48	56.3 (d)	4.01 (dd, 4.9, 7.8, Hz, 1H)	H47, H49
49	38.3 (d)	1.71 (m, 1H)	H48, H50, H50b, H52
50	22.8 (t)	1.38 (m, H)	H50b, H49, H51
		1.01 (m, 1H)	H50a, H49, H51
51	11.4 (q)	0.79 (t, 6.8 Hz, 3H)	H50a, H50b
52	15.8 (q)	0.79 (d, 6.8 Hz, 3H)	H49
53	n.o.	-	-

^aChemical shifts determined from 2D heteronuclear experiments

n.o. = not observed

Compound 9

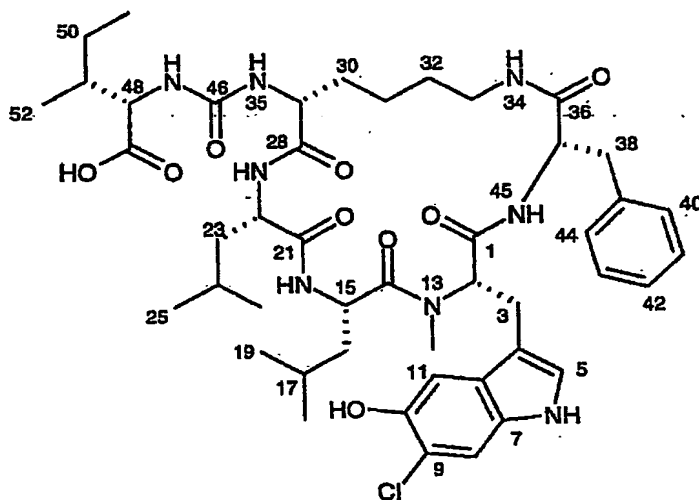


Table 9 ¹H (600 MHz), ¹³C (125 MHz), HMBC and COSY
NMR data for Compound 9 in d₆-DMSO

Atom No	¹³ C (mult) ^a	¹ H (mult, J Hz)	¹³ C-H correlations	COSY
N-Methyl tryptophan 1	169.5 (s)	-	-	-

2	60.8 (d)	4.69 (dd, 2.6, 10.4 Hz, 1H)	1	H3a, H3b
3	21.7 (t)	2.76 (m, 1H)	2, 4, 12	H2, H3b
		3.04 (m, 1H)	2, 4, 12	H2, H3a
4	108.9 (s)	-	-	-
5	124.3 (d)	6.88 (bs, 1H)	4, 7, 12	H6
6		10.66 (bs, 1H)	4, 5, 7, 12	H5
7	130.2 (s)	-	-	-
8	111.8 (d)	7.27 (s, 1H)	9, 10, 12	-
9	115.8 (s)	-	-	-
10	145.9 (s)	-	-	-
11	102.7 (d)	6.99 (s, 1H)	4, 7, 9, 10	-
12	126.1 (s)	-	-	-
NMe	27.4 (q)	1.91 (s, 3H)	2, 14	-
Leucine				
14	172.5 (s)	-	-	-
15	46.7 (d)	4.22 (ddd, 2.9, 4.9, 9.8 Hz, 1H)	-	H16a, H16b, H20
16	37.4 (t)	-0.49 (dd, 9.8, 9.8 Hz, 1H)	18	H15, H16b, H17
		0.95 (m, 1H)	-	H15, H16a, H17
17	23.1 (d)	1.40 (m, 1H)	-	H16a, H16b, H19, H18
18	19.7 (q)	0.25 (d, 6.8 Hz, 3H)	16, 17, 19	H17
19	22.3 (q)	0.42 (d, 6.8 Hz, 3H)	16, 17, 18	H17
20	-	8.47 (d, 4.3 Hz, 1H)	21	H15
leucine				
21	173.5 (s)	-	-	-
22	50.7 (d)	4.03 (td, 7.8, 6.9 Hz, 1H)	21, 23	H23, H27
23	39.7 (t)	1.46 (m, 2H)	-	H22, H24
24	23.3 (d)	1.67 (m, 1H)	15, 16	H23, H25, H26
25	21.6 (q)	0.82 (d, 7.0 Hz, 3H)	23, 24, 26	H24
26	22.8 (q)	0.88 (d, 7.0 Hz, 3H)	23, 24, 25	H24
27	-	6.86 (d, 6.9 Hz, 1H)	28	H22
lysine				
28	172.2 (s)	-	-	H30, H35
29	54.4 (d)	3.88 (ddd, 5.9, 6.8, 6.8 Hz, 1H)	28, 30, 31	H29, H31a, H31b
30	32.1 (t)	1.54 (m, 2H)	-	H30, H31b, H32
31	20.2 (t)	1.40 (m, 1H)	-	H30, H31a, H32
		1.10 (m, 1H)	-	H30, H22a, H23
32	28.1 (t)	1.42 (m, 2H)	-	H31a, H31b, H33a, H33b
33	38.3 (t)	2.84 (m, 1H)	-	H32, H33b, H34
		3.57 (m, 1H)	-	H32, H33a, H34
34	-	7.38 (dd, 1.2, 7.8 Hz, 1H)	-	H33a, H33b

35		6.35 (d, 6.8 Hz, 1H)	46	H29
phenylalanine				
36	171.4 (s)	-	-	-
37	54.5 (d)	4.52 (ddd, 2.9, 8.8, 11.7 Hz, 1H)	36	H38a, H38b, H45
38	37.9 (t)	2.74 (dd, 11.7, 13.7 Hz, 1H)	39, 40, 44	H37, H38b
		3.55 (dd, 2.9, 13.7 Hz, 1H)	28, 27, 30, 31, 38	H27, H38a
39	138.3 (s)	-	-	-
40	128.7 (d)	7.08 (d, 8.0 Hz, 1H)	42, 44	H41, H42
41	129.2 (d)	7.23 (dd, 8.0, 8.0 Hz, 1H)	39, 43	H40, H42
42	126.6 (d)	7.17 (t, 8.0 Hz, 1H)	40, 44	H41, H43, H40, H44
43	129.2 (d)	7.23 (dd, 8.0, 8.0 Hz, 1H)	39, 41	H42, H44
44	128.7 (d)	7.08 (d, 8.0 Hz, 1H)	40, 38, 42	H43, H42
45	-	8.71 (d, 8.8 Hz, 1H)	1	H37
46	157.0 (s)	-	-	-
isoleucine				
47	-	6.26 (d, 8.7 Hz, 1H)	-	H48
48	56.9 (d)	4.03 (dd, 5.9, 7.8, 7.8 Hz, 1H)	46, 49, 50, 52, 53	H47, H49
49	37.6 (d)	1.70 (m, 1H)	-	H48, H50b, H50a, H52
50	24.6 (t)	1.35 (m, 1H)	48, 49, 51, 52	H49, H50a, H50b, H51
		1.10 (m, 1H)	49, 51, 52	H49, H50a, H50b, H51
51	11.7 (q)	0.86 (t, 6.8 Hz, 3H)	49, 50	H50a, H50b
52	15.8 (q)	0.85 (d, 6.8 Hz, 3H)	48, 49, 50	H49
53	173.8 (s)	-	-	-

^aChemical shifts determined from 2D heteronuclear experiments

Compound 10

03-10-29

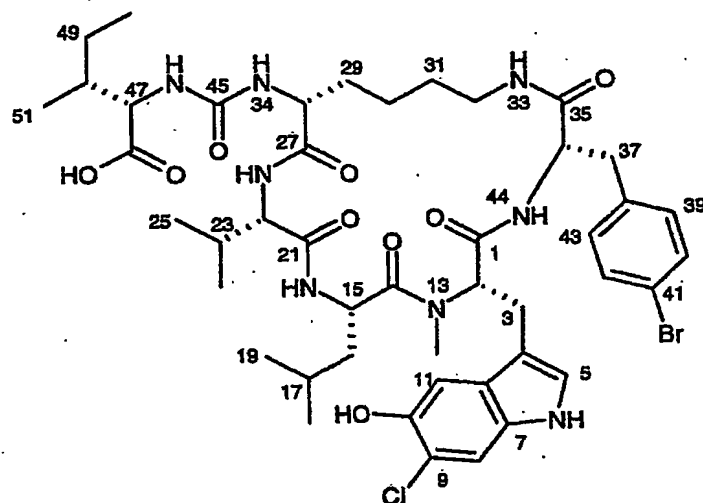


Table 10 ^1H (600 MHz), ^{13}C (125 MHz), HMBC and COSY
NMR data for Compound **10** in d_6 -DMSO

Atom No	^{13}C (mult) ^a	^1H (mult, J Hz)	^{13}C correlations	COSY
N-Methyl tryptophan				
1	169.8 (s)	-	-	-
2	60.9 (d)	4.66 (dd, 2.9, 10.7 Hz, 1H)	1, 3, 4, 14, 13-NMe	H3a, H3b
3	21.9 (t)	2.77 (m, 1H)	2, 4, 5	H2, H3b
		3.07 (m, 1H)	2, 4, 5	H2, H3a
4	109.3 (s)	-	-	-
5	126.1 (d)	6.89 (d, 2.0 Hz, 1H)	4, 7, 12	H6
6	-	10.68 (bs, 1H)	4, 5, 7, 12	H5
7	130.5 (s)	-	-	-
8	111.8 (d)	7.26 (s, 1H)	7, 9, 10, 12	-
9	115.8 (s)	-	-	-
10	146.2 (s)	-	-	-
11	103.4 (d)	6.98 (s, 1H)	4, 7, 9	-
12	126.8 (s)	-	-	-
NMe	27.3 (q)	1.97 (s, 3H)	2, 14	-
Leucine				
14	171.9 (s)	-	-	-
15	46.8 (d)	4.21 (ddd, 2.9, 4.9, 11.7 Hz, 1H)	-	H16a, H16b, H20
16	37.2 (t)	-0.48 (dd, 11.7, 11.7 Hz, 1H)	-	H15, H16b, H17
		0.95 (m, 1H)	-	H15, H16a, H17
17	23.3 (d)	1.40 (m, 1H)	-	H16a, H16b, H19, H18

18	19.5 (q)	0.27 (d, 6.8 Hz, 3H)	16, 17, 19	H17
19	21.3 (q)	0.41 (d, 6.8 Hz, 3H)	16, 17, 18	H17
20	-	8.42 (d, 4.9 Hz, 1H)	15, 16, 21	H15
leucine				
21	172.9 (s)	-	-	-
22	57.7 (d)	3.77 (dd, 6.8, 7.8 Hz, 1H)	21, 23, 24, 25	H23, H26
23	29.8 (t)	1.88 (m, 2H)	-	H22, H23, H24
24	18.9 (q)	0.84 (d, 7.0 Hz, 3H)	22, 23, 25	H23
25	18.9 (q)	0.93 (d, 7.0 Hz, 3H)	22, 23, 24	H23
26	-	6.74 (d, 6.9 Hz, 1H)	23, 28	H22
lysine				
27	172.2 (s)	-	-	-
28	54.5 (d)	3.84 (ddd, 5.9, 6.8, 6.8 Hz, 1H)	20, 28, 29, 45	H29, H34
29	31.5 (t)	1.54 (m, 2H)	-	H28, H30a, H30b
30	20.2 (t)	1.40 (m, 1H)	-	H29, H30b, H31
		1.10 (m, 1H)	-	H29, H30a, H31
31	28.2 (t)	1.42 (m, 2H)	-	H30a, H30b, H32a, H32b
32	38.3 (t)	2.85 (m, 1H)	-	H31, H32b, H33
		3.57 (m, 1H)	30, 31	H31, H32a, H33
33	-	7.46 (dd, 1.2, 7.0 Hz, 1H)	35	H32a, H32b
34	-	6.41 (d, 6.8 Hz, 1H)	29, 28, 45	H28
phenylalanine				
35	170.4 (s)	-	-	-
36	54.1 (d)	4.52 (ddd, 2.9, 8.8, 11.7 Hz, 1H)	35	H37a, H37b, H44
37	37.2 (t)	2.72 (dd, 11.7, 13.7 Hz, 1H)	36, 38, 39, 43	H36, H37b
		3.36 (dd, 2.9, 13.7 Hz, 1H)	36, 38, 39, 43	H36, H37a
38	137.9 (s)	-	-	-
39	131.4 (d)	7.01 (d, 7.8 Hz, 1H)	37, 41, 43	H40
40	130.4 (d)	7.37 (d, 7.8 Hz, 1H)	42, 38	H39
41	119.2 (s)	-	-	-
42	130.4 (d)	7.39 (d, 7.8 Hz, 1H)	40, 38	H43
43	131.4 (d)	7.08 (d, 7.8 Hz, 1H)	37, 39, 41	H42
44	-	8.81 (d, 8.8 Hz, 1H)	-	H36
45	157.3 (s)	-	-	-
isoleucine				
46	-	6.26 (d, 8.8 Hz, 1H)	45, 47	H47
47	57.2 (d)	4.04 (dd, 4.9, 8.8, 7.8 Hz, 1H)	45, 48, 49, 51, 52	H48, H46
48	37.2 (d)	1.70 (m, 1H)	-	H47, H49b, H49a
49	25.1 (t)	1.33 (m, 1H)	47, 48, 50, 51	H49a, H48, H50
		1.07 (m, 1H)	47, 48, 50, 51	H49b, H48, H50
50	11.4 (q)	0.83 (t, 6.8 Hz, 3H)	48, 49	H49a, H49b

51	15.8 (q)	0.83 (d, 6.8 Hz, 3H)	47, 48, 49	H48
52	174.5 (s)	-	-	-

^aChemical shifts determined from 2D heteronuclear experiments

EXAMPLE 2

This Example describes the isolation of Compound 11.

General Experimental Procedures

Water was Milli-Q filtered, while all other solvents used were Omnisolv. A Hypersil BDS basic C18 5uM, 21.2 mm x 150 mm, column were used for preparative HPLC. NMR spectra were recorded on a Varian Inova 600 or 500 MHz NMR spectrometer. Samples were dissolved in d₆-DMSO and chemical shifts were calculated relative to the solvent peak (DMSO ¹H δ 2.50 and ¹³C 39.5 ppm). Mass spectra were measured on a Fisons VG Platform II, using positive electrospray ionisation mode. The elution solvent was a mixture acetonitrile/water 50% at 0.1 ml/min.

Animal Material

Six sponge samples of *Candidaspongia flabellata* were collected by SCUBA diving at Outer Gneering, Sunshine Coast, Old Reef, Fairfax Is and Chauvel Reef, Queensland, Australia and voucher samples (G315106, G314580, G314025, G315402, G318260, G317513) were lodged at the Queensland Museum, Brisbane, Australia.

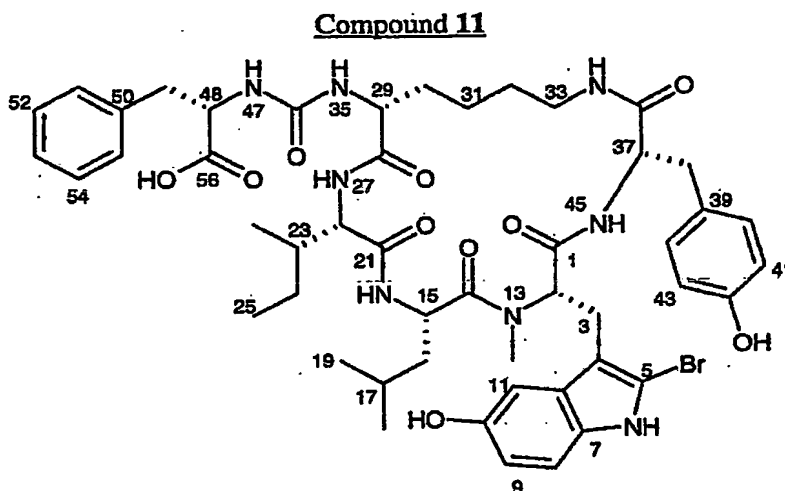
Extraction and Isolation

The freeze-dried sponge materials (529 g) were ground and exhaustively extracted with methanol to afford six methanol extracts. The methanol crude extracts underwent a series of partitions: MeOH/*n*-hexane, H₂O:MeOH(4:1)/DCM, H₂O:MeOH(4:1)/EtOAc. Bioactivity was spread in the H₂O:MeOH(4:1) and EtOAc layers. The H₂O:MeOH(4:1) and EtOAc layers were combined for all six biota and then partitioned with H₂O/butanol. The activity was in the butanol layer (900 mg), which then underwent countercurrent chromatography {H₂O/MeOH/EtOAc (4:1:5)}, upper layer mobile phase. The very early eluting fractions, 13-24, were combined (325 mg) and partitioned *n*-hexane:EtOAc:MeOH:H₂O (1:1:1:1). The bioactive aqueous layer (150 mg) was then chromatographed further by counter current chromatography {(CHCl₃:MeOH:H₂O

(7:13:8)), lower layer mobile phase. The early eluting active fractions, 25-32, were combined to give 85 mg of material. This underwent a final purification step by HPLC (Hypersil BDS C18) using a 30 min H₂O/MeCN gradient from H₂O (containing 1% TFA) to MeCN (containing 1% TFA). This yielded 0.4 mg of Compound 11 eluting after 18.2 mins.

Compound 11: MS: (positive ESI) $[M+H]^+$ m/z 1003.0 (100), 1004.4 (72), 1005.4 (75), 1006.3 (32). ¹H and ¹³C NMR (*d*₆-DMSO): see Table 11.

- 10 Compound 11 was also identified as a cyclic peptide after detailed studies, including ¹H, ¹³C, gHSQC, gHMBC, and gCOSY experiments.



15 Table 11 ¹H (600 MHz), ¹³C (125 MHz), HMBC and COSY NMR data for Compound 11 in *d*₆-DMSO

Atom No	¹³ C (mult) ^a	¹ H (mult, J Hz)	²³ J _{CH} correlations	COSY
N-Methyl tryptophan				
1	n.o.	-	-	-
2	60.0 (d)	4.70 (bd, 10.8 Hz, 1H)	-	H3a, H3b
3	22.4 (t)	2.71 (dd, 14.5, 10.8 Hz, 1H) 3.14 (d, 14.5 Hz, 1H)	-	H2, H3b H3a
4	n.o.	-	-	-
5	108.9 (s)	-	-	-

6	-	11.33 (s, 1H)	4, 7, 12	-
7	130.8 (s)	-	-	-
8	111.0 (d)	7.05 (bd, 8.0 Hz, 1H)	12, 10	H9
9	111.8 (d)	6.60 (bd, 8.0 Hz, 1H)	-	H8
10	150.8 (s)	-	-	-
11	101.8 (d)	6.82 (bs, 1H)	7, 10	-
12	128.1 (s)	-	-	-
NMe	28.5 (q)	2.10 (s, 3H)	2	-
Leucine				
14	172.4 (s)	-	-	-
15	46.8 (d)	4.16 (m, 1H)	-	H16a, H16b, H20
16	36.6 (t)	0.32 (bt, 11.0 Hz, 1H)	15	H16b, H17
		0.96 (m, 1H)	-	H15, H16a
17	22.4 (d)	*1.42 (m, 1H)	-	-
18	19.0 (q)	0.22 (d, 6.6 Hz, 3H)	16, 17, 19	H17
19	22.1 (q)	0.41 (d, 6.6 Hz, 3H)	16, 17, 18	H17
20	-	8.38 (d, 4.8 Hz, 1H)	14	H15
Isoleucine				
21	171.6 (s)	-	-	-
22	55.7 (d)	3.99 (t, 6.8 Hz, 1H)	23, 26	H23, H27
23	35.7 (d)	1.76 (m, 1H)	21	H22, H24a, H26
24	24.7 (t)	1.10 (m, 1H)	-	H23, H24b, H25
		*1.44 (m, 1H)	-	H24a, H25
25	11.2 (q)	0.85 (t, 7.2 Hz, 3H)	23, 24	H24a, H24b
26	14.2 (q)	0.81 (d, 6.6 Hz, 3H)	22	H23
27	-	6.78 (d, 6.8 Hz, 1H)	-	H22
Lysine				
28	172.4 (s)	-	-	-
29	54.3 (d)	3.85 (dddd, 7.0, 6.5, 5.0 Hz, 1H)	28	H30a, H30b, H35
30	31.0 (t)	1.52 (m, 1H)	-	H29, H31a
		1.60 (m, 1H)	-	H29, H31b
31	20.1 (t)	1.14 (m, 1H)	-	H30a
		1.25 (m, 1H)	-	H30b
32	26.6 (t)	1.38 (m, 1H)	-	H33b
		1.41 (m, 1H)	-	-
33	37.8 (t)	2.85 (m, 1H)	-	H34
		3.52 (m, 1H)	-	H34, H32a
34	-	7.35 (m, 1H)	-	H33a, H33b
35	-	6.48 (d, 7.0 Hz, 1H)	-	H29

Tyrosine				
36	n.o.	-	-	-
37	54.7 (d)	4.50 (ddd, 11.7, 9.0, 4.9 Hz, 1H)	-	H38a, H38b, H45
38	36.5 (t)	2.62 (bt, 13.0 Hz, 1H)	39	H37, H38b
		³ 3.23 (m, 1H)	39	H37, H38a
39	130.0 (s)	-	-	-
40	128.5 (d)	6.87 (d, 7.5 Hz, 1H)	38, 39, 42	H41
41	114.8 (d)	6.62 (d, 7.5 Hz, 1H)	40, 42, 44	H40
42	156.0 (s)	-	-	-
43	114.8 (d)	6.62 (d, 7.5 Hz, 1H)	40, 42, 44	H44
44	128.5 (d)	6.87 (d, 7.5 Hz, 1H)	38, 39, 42	H43
45	-	8.54 (d, 9.0 Hz, 1H)	-	H37
46	n.o.	-	-	-
Phenylalanine				
47	-	6.26 (d, 8.0 Hz, 1H)	-	H48
48	53.4 (d)	4.36 (ddd, 8.0, 7.5, 5.2 Hz, 1H)	56, 49	H49a, H49b, H47
49	37.2 (t)	2.86 (dd, 13.8, 7.5 Hz, 1H)	56, 55, 51, 50, 48	H48
		2.99 (dd, 13.8, 5.2 Hz, 1H)	56, 55, 51, 50, 48	H48
50	137.5 (s)	-	-	-
51	129.0 (d)	7.16 (d, 7.5 Hz, 1H)	53, 49	H52, H54
52	128.0 (d)	7.27 (t, 7.5 Hz, 1H)	50	H51, H55
53	126.2 (d)	7.20 (t, 7.5 Hz, 1H)	51, 55	-
54	128.0 (d)	7.27 (t, 7.5 Hz, 1H)	50	H51, H55
55	129.0 (d)	7.16 (d, 7.5 Hz, 1H)	53, 49	H52, H54
56	173.8 (s)	-	-	-
OH	-	8.71 (s, 1H)	-	-
OH	-	9.13 (s, 1H)	-	-

^a Chemical shift estimated from 2D NMR experiments

n.o. = not observed.

EXAMPLE 3

5 This Example describes the synthesis of Compound 12.

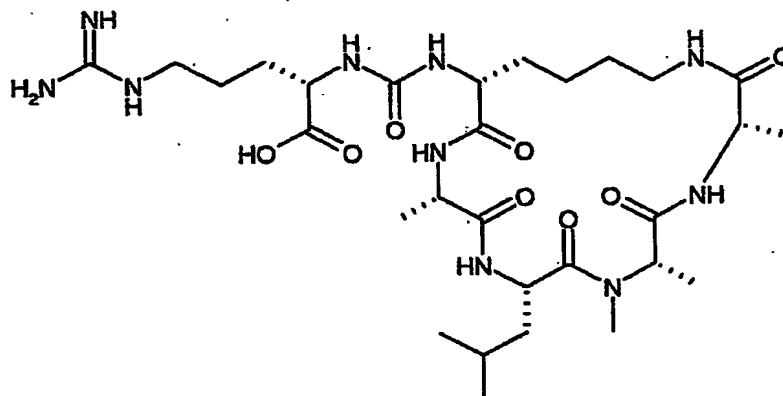
General Experimental Procedures

High resolution mass spectra were recorded on a Micromass LCT mass spectrometer equipped with an electrospray interface (LC-HRMS). ¹H NMR measurements were performed on Varian UNITY plus 400, 500 and 600 spectrometers, operating at ¹H

10

frequencies of 400, 500 and 600 MHz respectively. NMR spectra were recorded in d₆-DMSO with chemical shifts given in ppm with the solvent as internal standard.

Compound 12



5 Synthesis of Compound 12

Compound 12 was prepared according to a literature procedure (Marsh and Bradley, *J. Org. Chem.*, **1997**, *62*, 6199-6203) with the following modifications: Fmoc-L-Arg-*N*^{ω, ω'}-(Boc)₂-OH was first coupled to the resin/linker. After removal of the Fmoc group, the free amine was coupled with *N*^α-(4-nitrophenyloxycarbonyl)-*N*^ε-(9-fluorenylmethoxycarbonyl)-D-lysine allyl ester. Fmoc peptide synthesis continued on the side chain of the lysine residue using Fmoc-L-Ala followed by Fmoc-L-N-MeAla, Fmoc-L-Leu and Fmoc-L-Ala. Allyl ester and Fmoc removal was followed by cyclization and finally cleavage from the resin/linker. Purification of the residue by reversed-phase HPLC (Ace C8 column, linear gradient 5%→95% MeCN in 0.1 M aqueous NH₄OAc) gave

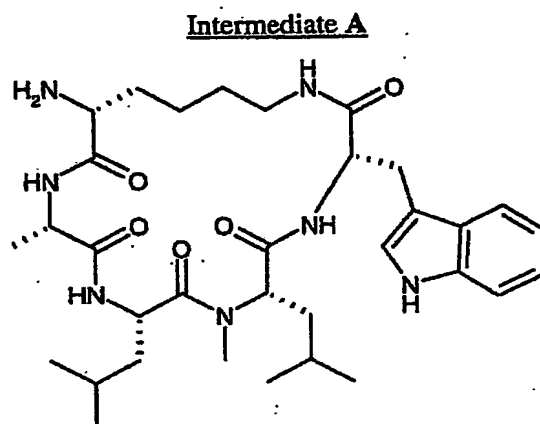
15 Compound 12 (1.8 mg, 1.3%).

¹H NMR (500 MHz, d₆-DMSO): δ 9.2 (broad s, 1H), 8.66 (d, 1H), 8.52 (d, 1H), 7.4-8.0 (broad signal, 4H), 7.47 (dd, 1H), 7.10 (d, 1H), 6.56 (d, 1H), 6.08 (d, 1H), 4.77-4.83 (m, 1H), 4.70-4.77 (m, 1H), 4.23 (qd, 1H), 4.07 (qd, 1H), 3.88-3.98 (m, 1H), 3.65-3.75 (m, 1H), 3.47-3.52 (m, 1H), 3.03 (broad t, 2H), 2.71-2.78 (m, 1H), 2.52 (s, 3H), 1.78-1.84 (m, 1H), 1.68-1.79 (m, 1H), 1.30-1.65 (m, 12H), 1.15-1.23 (m, 2H), 1.18 (two d, 6H), 0.94 (d, 3H), 0.93 (d, 3H), 0.89 (d, 3H), 0.88 (d, 3H).

HRMS (ESI) calculated for C₃₂H₅₉N₁₀O₈ 711.4517 (M+H)⁺, found 711.4525.

EXAMPLE 4

This Example describes the synthesis of Compounds 1 and 13 to 16.

Synthesis of Compound 1**5 a) Synthesis of Intermediate A**

TFA (2 mL) was added to Boc-D-Lys(Fmoc)-OAllyl (2.86 g, 5.6 mmol) and left to stand for 5 min. The TFA was then removed by a stream of dry nitrogen to afford H-D-Lys(Fmoc)-OAllyl which was dried on a high vacuum line for 2 h to remove all traces of TFA. 2-Chlorotrityl resin (1 g, 1.4 mmol) was pre-swelled in DCM (10 mL) for 1 h. The resin was drained and a solution of H-D-Lys(Fmoc)-OAllyl (2.30 g, 5.64 mmol) and DIEA (729 mg, 982 μ L, 5.64 mmol) in DCM (10 mL) was added and the reaction mixture shaken for 1 h. Further DIEA (1.46 g, 1.95 mL, 11.3 mmol) was added to the resin and the reaction mixture shaken for a further 1 h. Methanol (1 mL) was added to end-cap any unreacted resin and the reaction mixture shaken for a further 1 h. The resin was filtered and washed with DMF (2 x 5 mL), DCM (2 x 5 mL) and DMF (2 x 5 mL). The resin was subjected to Fmoc-solid phase peptide synthesis (SPPS) using the following conditions:

- (i) **Fmoc deprotection:** 20 % piperidine in DMF (2 x 10 mL) for 2 min followed by washing with DMF (4 x 5 mL), DCM (4 x 5 mL) and DMF (4 x 5 mL).
- (ii) **Coupling conditions:** In all couplings the solution of the coupling reagent is added to the Fmoc-amino acid. This solution is added to the resin followed by DIEA. (a) Fmoc-Trp(Boc)-OH (2.95 g, 5.6 mmol), HBTU (0.5 M solution, 11.2 mL) and DIEA (0.975 mL, 5.6 mmol) 20 min. (b) Fmoc-

5 *N*-Me-Leu-OH (2.06 g, 5.6 mmol), HBTU (0.5 M solution, 11.2 mL) and DIEA (0.975 mL, 5.6 mmol) 20 min. (c) Fmoc-Leu-OH (1.98 g, 5.6 mmol), HOBt (756 mg, 5.6 mmol), HATU (2.13 g, 5.6 mmol) and DIEA (314 μ L, 1.8 mmol) in DMF (10 mL) 3 h. (d) Fmoc-Ala-OH (1.74 g, 5.6 mmol), HBTU (0.5 M solution, 11.2 mL) and DIEA (0.975 mL, 5.6 mmol) 20 min. Following all couplings the resin was filtered and washed with DMF (4 x 5 mL), DCM (4 x 5 mL) and DMF (4 x 5 mL). All couplings except for (c) were monitored using the ninhydrin test, coupling (c) was monitored using a bromophenol blue test. All couplings were also monitored by MS by
 10 cleaving a small amount of resin (5 mg) with 100 % TFA for 5 min, the filtrate from the resin was then analysed by MS.

A solution of Pd(PPh₃)₄ (1.62 g, 1.4 mmol) and dimedone (1.96 g, 14 mmol) in THF:DCM (1:1, 50 mL) was sparged with nitrogen gas for 10 min., added to the resin and the mixture shaken for 16 h. The reaction mixture was filtered and washed with DCM (3 x 5 mL),
 15 DMF (3 x 5 mL) a solution of 0.5% DIEA and 0.5% diethyldithiocarbamic acid sodium salt in DMF (3 x 5 mL) and DMF (3 x 5 mL). The resin was treated with 20 % piperidine in DMF (2 x 10 mL) for 2 min. followed by washing with DMF (4 x 5 mL), DCM (4 x 5 mL), 10% pyridinium hydrochloride in DCM:DMF (1:1, 4 x 5 mL) and DMF (4 x 5 mL). A solution of PyBroP (718 mg, 1.54 mmol) and DIEA (1 mL, 5.74 mmol) in DCM:DMF
 20 (1:1, 10 mL) was added to the resin and the mixture shaken for 3 h after which a ninhydrin test was negative. The cyclic peptide was cleaved from the resin by treatment with 50% TFA in DCM (20 mL) for 1 h. The resin was filtered, washed with TFA (2 x 5 mL) and DCM (2 x 5 mL), concentrated to dryness, re-dissolved in MeCN:H₂O (0.1% TFA) and lyophilised to afford Intermediate A (435 mg, 38%).

25 b) Allyl-*N*²-[(9H-fluoren-9-ylmethoxy)carbonyl]-*N*⁵-[iminol(2,2,4,6,7-pentamethyl-2,3-dihydro-1-benzofuran-5-yl)amino]methyl}ornithinate

30 *N*²-[(9H-fluoren-9-ylmethoxy)carbonyl]-*N*⁵-[iminol(2,2,4,6,7-pentamethyl-2,3-dihydro-1-benzofuran-5-yl)amino]methyl}ornithine (1.0g, 1.54 mmol) was dissolved in DMF (5 mL). Caesium carbonate (377 mg, 1.16 mmol) was added and the reaction mixture stirred for 1 h. Allyl bromide (0.913 mL, 10.8 mmol) was then added and stirring was continued for a further 1 h resulting in a milky white solution. Water (25 mL) was

added and the reaction mixture acidified with 2M KHSO₄. DCM (50 mL) was added and the phases separated. The aqueous phase was washed with DCM (2 x 50 mL) and the combined organics washed with brine (50 mL), dried (MgSO₄), filtered and concentrated to dryness to afford allyl-*N*²-[(9H-fluoren-9-ylmethoxy)carbonyl]-*N*⁵-{imino[(2,2,4,6,7-pentamethyl-2,3-dihydro-1-benzofuran-5-yl)amino]methyl}ornithinate as colourless foam (857 mg, 81%).

¹HNMR (CDCl₃, 500 MHz): δ 1.43 (s, 6H), 1.59 (m, 2H), 1.73 (m, 1H), 1.86 (m, 1H), 2.09 (s, 3H), 2.52 (s, 3H), 2.61 (s, 3H), 2.91 (s, 2H), 3.22 (m, 2H), 4.17 (t, *J* 7 Hz, 1H), 4.32 (m, 1H), 4.37 (m, 1H), 4.59 (br d, *J* 4.5 Hz, 2H), 5.21 (d, *J* 10.5 Hz, 1H), 5.30 (d, *J* 10 Hz, 1H), 5.83 (m, 1H), 5.88 (m, 1H), 6.26 (br s, 1H), 6.35 (br s, 2H), 7.26 (t, *J* 7.5 Hz, 2H), 7.37 (t, *J* 7.5 Hz, 2H), 7.57 (m, 2H), 7.74 (d, *J* 7.5 Hz, 2H).

¹³CNMR (CDCl₃, 125 MHz): δ 12.68, 18.22, 19.54, 25.69, 28.78, 29.93, 40.96, 43.43, 47.36, 53.72, 54.10, 66.23, 67.39, 86.63, 117.78, 119.12, 120.19, 124.93, 125.40, 127.34, 127.96, 131.79, 132.47, 133.17, 138.54, 141.49, 143.97, 144.08, 156.63, 159.03, 171.42).

MS: (positive ESI) [M+H]⁺ *m/z* 689.

c) Allyl-*N*⁵-[[(4-ethyl-2,2,6,7-tetramethyl-2,3-dihydro-1-benzofuran-5-yl)amino](imino)methyl]-*N*²-[(4-nitrophenoxy)carbonyl]ornithinate

Allyl-*N*²-[(9H-fluoren-9-ylmethoxy)carbonyl]-*N*⁵-{imino[(2,2,4,6,7-pentamethyl-2,3-dihydro-1-benzofuran-5-yl)amino]methyl}ornithinate (800 mg, 1.16 mmol) was dissolved in DMF (4 mL). Piperidine (1 mL) was added, and the reaction mixture was stirred at room temperature for 30 min and then concentrated. The resulting residue was dissolved in DCM (9 mL) and added to a suspension of 4-nitrophenylchloroformate (370 mg, 1.85 mmol) and pyridine (750 μL, 9.3 μmol) in DCM (6 mL) with cooling in an ice-salt bath. After stirring for 2.5 h, 1M KHSO₄ (20 mL) was added, the organic layer separated and the aqueous phase extracted with DCM (4 x 20 mL). The combined organic extracts were dried (MgSO₄), filtered, concentrated and the resulting residue purified by flash chromatography on silica gel (100% Hexane to 7:3 EtOAc:hexane) to afford allyl-*N*⁵-[[(4-ethyl-2,2,6,7-tetramethyl-2,3-dihydro-1-benzofuran-5-yl)amino](imino)methyl]-*N*²-[(4-nitrophenoxy)carbonyl]ornithinate (138 mg, 18 %).

¹HNMR (CDCl₃, 500 MHz): δ 1.42 (s, 6H), 1.62 (m, 2H), 1.79 (m, 1H), 1.89 (m, 1H), 2.04 (s, 3H), 2.48 (s, 3H), 2.55 (s, 3H), 2.90 (s, 2H), 3.20 (m, 2H), 4.30 (m, 1H), 4.60 (br

d, J 4.5 Hz, 2H), 5.22 (d, J 10.5 Hz, 1H), 5.29 (d, J 17 Hz, 1H), 5.86 (m, 1H), 6.25 (br s, 1H), 6.33 (br s, 1H), 6.50 (br d, J 6.5 Hz, 1H), 6.90 (d, J 7.5 Hz, 1H), 7.25 (d, J 8 Hz, 2H), 8.05 (d, J 7.5 Hz, 1H), 8.15 (d, J 8 Hz, 2H).

^{13}C NMR (CDCl_3 , 125 MHz): δ 12.63, 18.16, 19.45, 25.74, 28.76, 29.44, 40.8, 43.41,

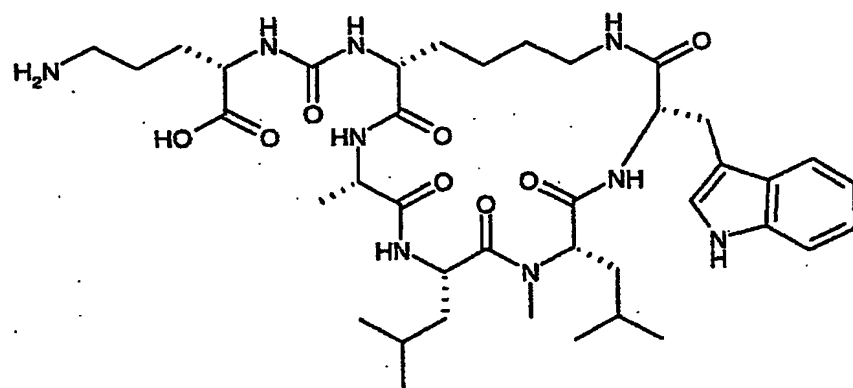
5 54.41, 66.39, 86.71, 115.99, 117.78, 119.21, 122.22, 124.97, 125.23, 126.22, 131.66, 132.40, 133.02, 138.43, 140.75, 144.97, 153.45, 156.06, 156.67, 159.04, 163.07, 163.80, 171.6.

MS: (positive ESI) $[\text{M}+\text{H}]^+$ m/z 632.

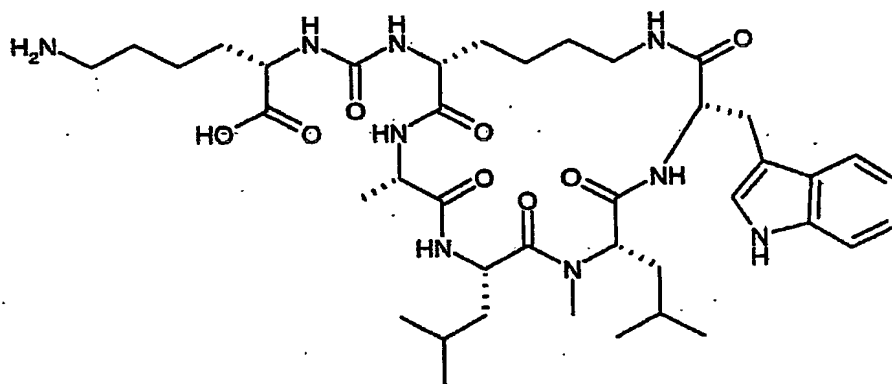
10 d) Compound 1.

Intermediate A (49.9 mg, 0.08 mmol) was dissolved in DMF (8 mL). Allyl- N^5 -[[[(4-ethyl-2,2,6,7-tetramethyl-2,3-dihydro-1-benzofuran-5-yl)amino](imino)methyl]- N^2 -[(4-nitrophenoxy)carbonyl]ornithinate (60.6 mg, 0.096 mmol) was added, followed by DIEA (17 μL , 0.096 mmol) and the reaction mixture stirred at room temperature for 16 h.

15 The reaction mixture was concentrated to give the crude urea. A solution of palladium (tetrakis)triphenylphosphine (8 mg, 0.0072 mmol) and dimedone (25 mg, 0.18 mmol) in THF:DCM (1:1, 5 mL) was sparged with dry nitrogen and then added via canula to the urea and stirred at room temperature overnight to afford the crude carboxylic acid. The carboxylic acid was dissolved in DCM (1 mL), and *p*-Cresol (340 μL) and TFA (250 μL)
20 were added and the reaction mixture stirred at room temperature for 20 h to afford crude Compound 1. The reaction mixture was purified by reverse phase HPLC (YMC basic semi prep column, linear gradient 65% Water (1% TFA) 35% MeCN (1% TFA) \rightarrow 100% MeCN (1% TFA)) to afford Compound 1 (11.3 mg, 17%). NMR and MS data were found to be identical with an authentic sample.

Compound 13Synthesis of Compound 13

Compound 13 was synthesised using a procedure similar to the procedure for
 5 Compound 1, starting from Intermediate A and N^2 -[(benzyloxy)carbonyl]- N^5 -(*tert*-
 butoxycarbonyl)ornithine. HRMS $C_{39}H_{61}N_9O_8$ 822.4280 (M+H)⁺, found 822.4262.

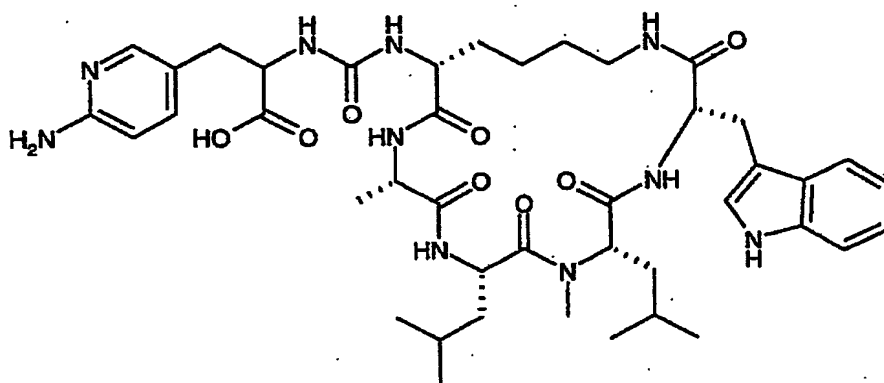
Compound 1410 Synthesis of Compound 14

Compound 14 was synthesised using a procedure similar to the procedure for Compound 1,
 starting from Intermediate A and *tert*-butyl N^6 -(*tert*-butoxycarbonyl)-L-lysinate.

¹H NMR (500 MHz, CD₃OD): δ 8.98 (d, 1H), 8.71 (d, 1H), 7.95 (dd, 1H), 7.79 (d, 1H),
 7.64 (d, 1H), 7.31 (d, 1H), 7.08 (t, 1H), 7.01 (t, 1H), 6.78 (s, 1H), 5.00-4.88 (m, 2H), 4.78-
 15 4.70 (m, 1H), 4.36-4.23 (m, 2H), 4.19-4.13 (m, 1H), 3.88-3.77 (m, 1H), 3.55 (dd, 1H),
 3.04-2.86 (m, 4H), 2.03-1.88 (m, 3H), 1.85 (s, 3H), 1.84-1.66 (m, 6H), 1.66-1.57 (m, 3H),

1.52 (d, 3H), 1.56-1.44 (m, 3H), 1.42-1.30 (m, 3H), 1.04 (two d, 6H), 0.95 (two d, 6H).
HRMS (ESI) calculated for $C_{40}H_{64}N_9O_8$ 798.4878 ($M+H$)⁺, found 798.4858.

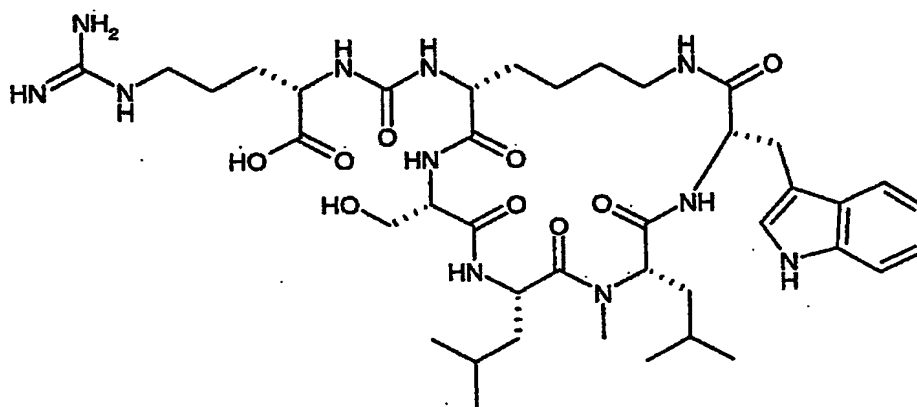
Compound 15



Synthesis of Compound 15

Compound 15 was synthesised using a procedure similar to the procedure for Compound 1, starting from Intermediate A and 3-{6-[(*tert*-butoxycarbonyl)amino]pyridin-3-yl}alanine (WO 01/02364). HRMS $C_{42}H_{61}N_{10}O_8$ 833.4674 ($M+H$)⁺, found 833.4678.

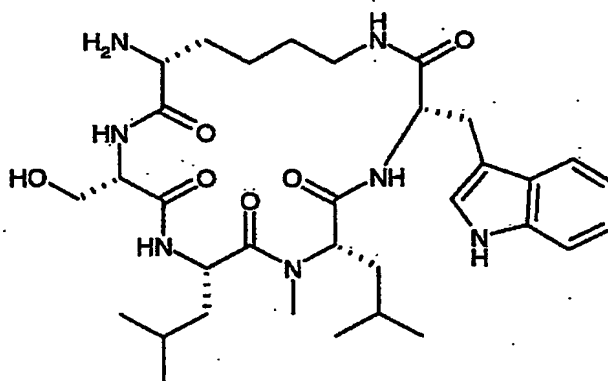
Compound 16



Synthesis of Compound 16

a) Synthesis of Intermediate B

Intermediate B was synthesised using a procedure similar to the procedure for Intermediate A.

Intermediate Bb) Synthesis of Compound 16

Compound 16 was synthesised according to the procedure for Compound 1,
 5 starting from Intermediate B.

¹H NMR (500 MHz, d₆-DMSO): δ 12.70 (broad s, 1H), 10.83 (s, 1H), 8.86 (d, 1H), 8.47 (d, 1H), 7.70-7.79 (m, 3H), 7.57 (t, 1H), 7.46 (d, 1H), 7.45 (dd, 1H), 7.35 (d, 1H), 7.28 (d, 1H), 7.02 (dd, 1H), 6.96 (dd, 1H), 6.81 (broad s, 1H), 6.47 (d, 1H), 6.46 (d, 1H), 4.82 (m, 1H), 4.74-4.75 (ddd, 1H), 4.43 (ddd, 1H), 4.22-4.24 (m, 1H), 4.13 (ddd, 1H), 4.02 (ddd, 1H), 3.78 (dd, 1H), 3.71 (dd, 1H), 3.60 (m, 1H), 3.35 (m, 1H), 3.11 (dt, 2H), 2.86-2.92 (m, 1H), 2.78-2.80 (m, 1H), 1.83 (s, 3H), 1.79-1.83 (m, 1H), 1.52-1.56 (m, 1H), 1.57-1.60 (m, 1H), 1.60-1.64 (m, 3H), 1.69-1.70 (m, 1H), 1.42-1.48 (m, 5H), 1.33-1.36 (m, 1H), 1.22-1.25 (m, 2H), 1.18-1.20 (m, 1H), 0.95 (d, 3H), 0.91 (d, 3H), 0.89 (d, 3H), 0.85 (d, 3H).

HRMS C₄₀H₆₄N₁₁O₉ 842.4888 (M+H)⁺, found 842.4885.

EXAMPLE 5

The activities of certain Examples in the assay described in: Dirk Hendriks, Simon Scharpé and Marc van Sande, Clinical Chemistry, 31, 1936-1939 (1985), using a substrate concentration of 4 mM, are presented in Table I below.

TABLE I

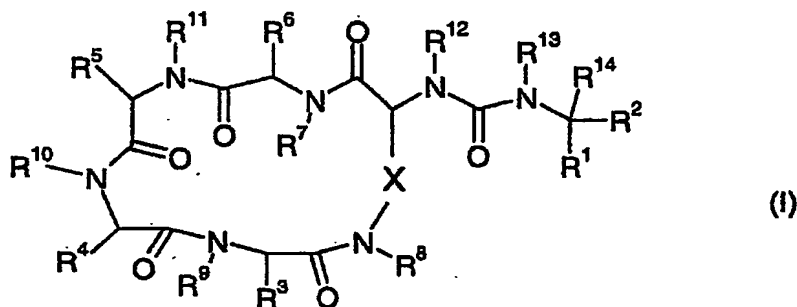
Compound No.	IC ₅₀
5	0.1 μM
8	2.5 μM
12	0.2 μM

Abbreviations

EtOAc = ethyl acetate
DCCC = droplet counter current chromatography
MeOH = methanol
Leu = leucine
DMSO = dimethyl sulfoxide
HPLC = high pressure liquid chromatography
RPHPLC = reverse phase high pressure liquid chromatography
Boc = *tert*-butoxycarbonyl
Fmoc = (9H-fluoren-9-ylmethoxy)carbonyl
gHMBC = gradient heteronuclear multiple bond correlation
gCOSY = gradient correlated spectroscopy
gHSQC = gradient heteronuclear single quantum coherence
CPC = centrifugal partition chromatography
DIEA = diisopropyl ethyl amine
HATU = *O*-(7-Azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate
HBTU = *O*-Benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate
THF = tetrahydrofuran
DMF = *N,N*-dimethylformamide
Trp = tryptophan
Lys = lysine
TFA = trifluoroacetic acid
DCM = dichloromethane
MeCN = acetonitrile
Ala = alanine
Arg = Arginine

CLAIMS

1. The use of a compound of formula (I):



wherein:

- 5 X is $(CH_2)_m Y(CH_2)_n$;
 m and n are, independently, 1, 2, 3, 4, 5 or 6; provided that m + n is not more than 6;
 Y is a bond, O, $S(O)_p$, or S-S;
 R¹ is CO_2R^{15} or a carboxylic acid isostere such as $S(O)_2OH$, $S(O)_2NHR^{15}$,
 10 $PO(OR^{15})OH$, $PO(OR^{15})NH_2$, $B(OR^{15})_2$, $PO(R^{15})OH$, $PO(R^{15})NH_2$ or tetrazole;
 R², R³, R⁴, R⁵ and R⁶ are, independently, hydrogen, C₁₋₆ alkyl (optionally substituted by halogen, hydroxy, cyano, SH, $S(O)_3H$, $S(O)_3(C_{1-6} \text{ alkyl})$, $OC(O)(C_{1-4} \text{ alkyl})$, CF_3 , C₁₋₄ alkoxy, OCF_3 , $COOH$, $CONH_2$, $CONH(C_{1-6} \text{ alkyl})$, NH_2 , $CNH(NH_2)$, or $NHCNH(NH_2)$), C₃₋₆ cycloalkyl(C₁₋₄)alkyl (wherein the cycloalkyl ring is optionally substituted by halogen, hydroxy, cyano, C₁₋₄ alkyl, CF_3 , C₁₋₄ alkoxy, OCF_3 , NH_2 , $CNH(NH_2)$ or $NHCNH(NH_2)$), heterocyclyl(C₁₋₄)alkyl (wherein the heterocyclyl ring is optionally substituted by halogen, hydroxy, cyano, C₁₋₄ alkyl, CF_3 , C₁₋₄ alkoxy, OCF_3 , NH_2 , $CNH(NH_2)$ or $NHCNH(NH_2)$), phenyl(C₁₋₄)alkyl (wherein the phenyl ring is optionally substituted by halogen, hydroxy, cyano, C₁₋₄ alkyl, CF_3 , C₁₋₄ alkoxy, OCF_3 , NH_2 , $CNH(NH_2)$ or $NHCNH(NH_2)$) or heteroaryl(C₁₋₄)alkyl (wherein the heteroaryl ring is optionally substituted by halogen, hydroxy, cyano, C₁₋₄ alkyl, CF_3 , C₁₋₄ alkoxy, OCF_3 , NH_2 , $CNH(NH_2)$ or $NHCNH(NH_2)$);
 15 p and q are, independently, 0, 1 or 2;
 R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹² and R¹³ are, independently, H or C₁₋₄ alkyl;
 R¹⁴ is H or C₁₋₄ alkyl; and,

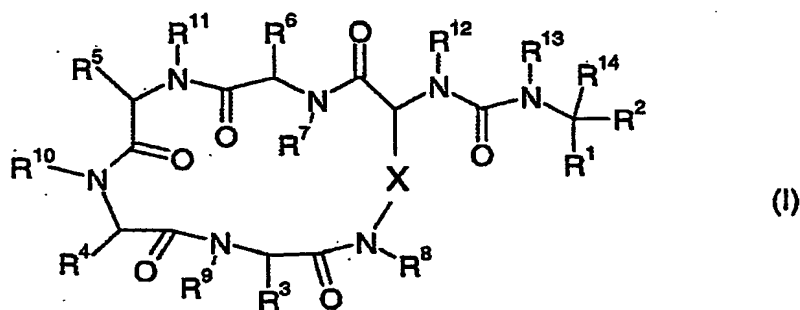
R¹⁵ is H or C₁₋₄ alkyl;

or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt;
in a method of manufacturing a medicament for the treatment or prophylaxis of a
condition wherein inhibition of carboxypeptidase U is beneficial, for example in the
treatment or prophylaxis of: thrombosis and/or hypercoagulability in blood and/or
tissues; atherosclerosis; adhesions; dermal scarring; cancer; fibrotic conditions;
inflammatory diseases; conditions which benefit from maintaining or enhancing
bradykinin levels in the body of a mammal; protein C resistance; inherited or
acquired deficiencies in antithrombin III, protein C, protein S or heparin cofactor II;
circulatory or septic shock; circulating antiphospholipid antibodies;
hyperhomocysteinemia; heparin induced thrombocytopenia; defects in fibrinolysis;
venous thrombosis; pulmonary embolism; arterial thrombosis; systemic embolism
usually from the atrium during atrial fibrillation or from the left ventricle after
transmural myocardial infarction; the prophylaxis of re-occlusion and restenosis
after thrombolysis; percutaneous trans-luminal intervention (PTI) and coronary
bypass operations; the prevention of re-thrombosis after microsurgery and vascular
surgery in general; disseminated intravascular coagulation caused by bacteria,
multiple trauma, intoxication or any other mechanism; fibrinolytic treatment when
blood is in contact with foreign surfaces in the body, such as vascular grafts,
vascular stents, vascular catheters, mechanical and biological prosthetic valves or
any other medical device; fibrinolytic treatment when blood is in contact with
medical devices outside the body, such as during cardiovascular surgery using a
heart-lung machine or in haemodialysis; prophylaxis of atherosclerotic progression
and/or transplant rejection in patients subject to organ transplantation, for example
renal transplantation; inhibiting tumor maturation and progression; any condition in
which fibrosis is a contributing factor; inflammation; neurodegenerative diseases
such as Alzheimers and Parkinsons; or conditions known to benefit from
maintaining or enhancing bradykinin levels.

2. A method for treatment or prophylaxis of conditions where inhibition of
carboxypeptidase U is beneficial, comprising administering to a mammal, including

man, in need of such treatment an effective amount of a compound of formula (I) as defined in claim 1.

3. A compound of formula (I):



wherein:

X is $(CH_2)_4$;

R^1 is CO_2R^{15} ;

R^2 is straight-chain C_{1-6} alkyl substituted at its terminus by NH_2 , $CNH(NH_2)$ or

$NHCNH(NH_2)$; C_{3-6} cycloalkyl substituted by NH_2 , $CNH(NH_2)$ or $NHCNH(NH_2)$;

heterocyclyl containing at least one nitrogen atom; non-nitrogen containing

heterocyclyl substituted with NH_2 , $CNH(NH_2)$ or $NHCNH(NH_2)$; heteroaryl

substituted with NH_2 , $CNH(NH_2)$ or $NHCNH(NH_2)$; phenyl substituted with NH_2 ,

$CNH(NH_2)$ or $NHCNH(NH_2)$; heteroaryl(C_{1-4})alkyl substituted with NH_2 ,

$CNH(NH_2)$ or $NHCNH(NH_2)$; phenyl(C_{1-4})alkyl substituted with NH_2 , $CNH(NH_2)$

or $NHCNH(NH_2)$; or C_{3-6} cycloalkyl(C_{1-4})alkyl substituted with NH_2 , $CNH(NH_2)$

or $NHCNH(NH_2)$; all of the above rings being optionally further substituted by one

or more of: halogen, hydroxy, cyano, C_{1-4} alkyl, CF_3 , C_{1-4} alkoxy or OCF_3 ;

one of R^3 , R^4 , R^5 and R^6 is independently, hydrogen, heteroaryl(C_{1-4})alkyl (wherein

the heteroaryl ring is optionally substituted by halogen, hydroxy, cyano, C_{1-4} alkyl,

CF_3 , C_{1-4} alkoxy, OCF_3 , NH_2 , $CNH(NH_2)$ or $NHCNH(NH_2)$); and the others are,

independently, hydrogen, C_{1-6} alkyl (optionally substituted by halogen, hydroxy,

cyano, SH , $S(O)_3H$, $S(O)_q(C_{1-6}$ alkyl), $OC(O)(C_{1-4}$ alkyl), CF_3 , C_{1-4} alkoxy, OCF_3 ,

$COOH$, $CONH_2$, $CONH(C_{1-6}$ alkyl), NH_2 , $CNH(NH_2)$, or $NHCNH(NH_2)$), C_{3-6}

cycloalkyl(C_{1-4})alkyl (wherein the cycloalkyl ring is optionally substituted by

halogen, hydroxy, cyano, C_{1-4} alkyl, CF_3 , C_{1-4} alkoxy, OCF_3 , NH_2 , $CNH(NH_2)$ or

NHCNH(NH₂)), heterocyclyl(C₁₋₄)alkyl (wherein the heterocyclyl ring is optionally substituted by halogen, hydroxy, cyano, C₁₋₄ alkyl, CF₃, C₁₋₄ alkoxy, OCF₃, NH₂, CNH(NH₂) or NHCNH(NH₂)), phenyl(C₁₋₄)alkyl (wherein the phenyl ring is optionally substituted by halogen, hydroxy, cyano, C₁₋₄ alkyl, CF₃, C₁₋₄ alkoxy, OCF₃, NH₂, CNH(NH₂) or NHCNH(NH₂)) or heteroaryl(C₁₋₄)alkyl (wherein the heteroaryl ring is optionally substituted by halogen, hydroxy, cyano, C₁₋₄ alkyl, CF₃, C₁₋₄ alkoxy, OCF₃, NH₂, CNH(NH₂) or NHCNH(NH₂));

p and q are, independently, 0, 1 or 2;

R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹² and R¹³ are, independently, H or C₁₋₄ alkyl;

R¹⁴ is H or C₁₋₄ alkyl; and,

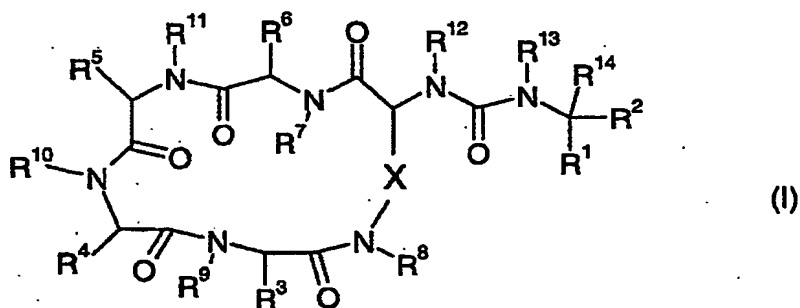
R¹⁵ is H or C₁₋₄ alkyl;

or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt.

4. A pharmaceutical formulation containing a compound of formula (I) as described in claim 1 as active ingredient in combination with a pharmaceutically acceptable adjuvant, diluent or carrier.
5. A pharmaceutical formulation containing a compound of formula (I) as claimed in claim 3 as active ingredient in combination with a pharmaceutically acceptable adjuvant, diluent or carrier.

ABSTRACT
CHEMICAL COMPOUNDS

The use of a compound of formula (I):



in a method of manufacturing a medicament for the treatment or prophylaxis of a condition wherein inhibition of carboxypeptidase U is beneficial; specified compounds of formula (I) and compositions comprising a compound of formula (I) and a pharmaceutically acceptable adjuvant, diluent or carrier.

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